

ACTA MEDICA SCANDINAVICA

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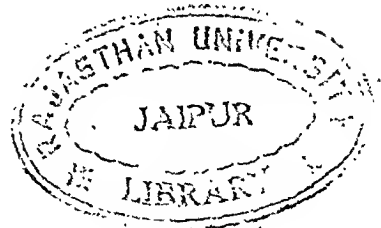
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De l'Institut Clinico-Médical A de l'Hôpital Filantropia (1-ère Clinique médicale de l'Université de Bucarest) Directeur: Prof. D. Danielopolu.

Recherches sur le mécanisme de l'immunité, de l'anaphylaxie et des maladies spécifiques (maladie du sérum, maladies infectieuses).

Phylaxie, paraphylaxie et choc paraphylactique acétylcholinique.

2-ème Mémoire.

Le phénomène de l'acétylcholinogénèse et le phénomène de décholinisation tissulaire. Action d'une substance étrangère introduite dans l'organisme.

Action acétylcholinergique des antigènes et de l'acide p-amino-benzoïque.

Par

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(Ce travail est parvenu à la rédaction le 3 Février 1944.)

Nous prouvons par de nombreux arguments que l'état d'anaphylaxie (que nous appelons paraphylaxie) est un état végétatif anormal. Le tonus des organes végétatifs est modifié. Leur réactivité est aussi anormale, comme le prouvent la réaction à l'adrénaline, à l'éserine, à l'atropine, un réflexe végétatif, etc. Nous prouvons aussi que le choc anaphylactique (que nous appelons *choc paraphylactique acétylcholinique*) est composé de phénomènes végétatifs: l'inhibition cardiaque, l'hypotension et l'état de collapsus, la bronchoconstriction, l'hypermotilité digestive, utérine et vésicale, etc. sont des phénomènes végétatifs. Même les convulsions ont une base végétative, l'acétylcholine jouant un rôle considérable dans les modifications du tonus de la musculature volontaire. Nombreux ont été les travaux qui ont signalé une modification dans

l'excitabilité des nerfs végétatifs pendant le choc anaphylactique. Certaines modifications du sang ressemblent à celles que nous trouvons dans certains états végétatifs anormaux. On s'est servi aussi des épreuves végétatives, qui par le fait que les auteurs ne connaissaient pas d'une manière exacte l'action des substances à action végétative qu'on employait, ont conduit forcément à des résultats tout à fait contradictoires. Il y eut alors des auteurs qui ont affirmé que le choc anaphylactique et l'anaphylaxie n'ont rien à faire avec la vie végétative. Et cela malgré que les phénomènes principaux étaient d'ordre végétatif. C'est que la physiologie du système végétatif était ignorée. Nous avons commencé nos recherches sur l'anaphylaxie en 1908, à une époque où la physiologie de ce système n'était nullement précisée. Nous n'avons rien compris alors en examinant les résultats de nos recherches. Et ce n'est qu'après 20 années de recherches sur le système végétatif, et spécialement sur les médiateurs chimiques, après avoir introduit dans la pratique d'autres épreuves végétatives et après avoir établi les trois lois fondamentales qui régissent la physiologie de ce système, que nous avons pu en reprenant nos recherches sur l'immunité, commencé à comprendre le mécanisme des phénomènes. Ce n'est qu'en 1931 ¹ que nous avons pu nous rendre compte que le choc dit anaphylactique est un choc acétylcholinique.

Les auteurs qui ont étudié le système végétatif dans l'anaphylaxie sont partis tous de l'idée, très erronée, que tout doit se produire par l'intermédiaire de ce système. Dans la conception classique que la sympathine et l'acétylcholine ne pouvaient être produites que par le sympathique ou le parasympathique et personne ne pouvait expliquer le mécanisme du choc anaphylactique produit sur l'organe isolé, séparé de ses nerfs. *Et c'est le fait établi pour la première fois par nous, que les médiateurs chimiques peuvent être libérés dans la cellule de l'organe terminal par des facteurs étrangers qui agissent en dehors de toute action nerveuse et spécialement l'action acétylcholinergique des antigènes, qui nous a permis de formuler une nouvelle conception sur la production des anticorps, sur l'immunité et sur les phénomènes produits à côté de l'immunité, qu'on a appelé anaphylaxie et que nous appelons paraphylaxie.*

¹ D. Danielopolu: Arch. méd. chir. de l'appareil respiratoire. Masson 1931
— Congrès de l'asthme du Mont-Dore, 1932

Avant d'exposer l'action acétylcholinergique des antigènes nous résumerons notre conception personnelle sur le cycle d'évolution des médiateurs chimiques, sur l'action des substances étrangères antigéniques et non antigéniques introduites dans l'organisme.

A. Rôle physiologique de l'adrénaline, de la sympathine et de l'acétylcholine. Préadrénalinémie et précholinémie permanentes. Adrélinémie et acétylcholinémie transitoires.

Les recherches que nous avons poursuivies durant de longues années, nous ont permis d'arriver à une conception personnelle sur le rôle physiologique des médiateurs chimiques.

Les cellules terminales contiennent dans leur protoplasme deux substances que nous avons appelées Complexe adrénalinique (CA) ou Préadrénaline et Complexe acétylcholinique (CACH) ou Précholine.

Ces substances n'ont aucune action excitatrice ou inhibitrice. Le CA entretient la réactivité des organes à l'influx sympathique (S) et sert de présubstance dont l'influx de ce nerf tire la sympathine efficiente (SyE); le CACH entretient la réactivité des organes pour le parasympathique (P) et sert de présubstance dont le parasympathique tire l'acétylcholine efficiente (AChE).

D'autres facteurs que les nerfs peuvent transformer le CA en SyE et le CACH en AChE. D'un autre côté, le CA entretient la réactivité des organes pour tout facteur qui agit comme le P.

Voici ce que nous avons établi au sujet du cycle de l'adrénaline, de la sympathine et de l'acétylcholine (fig. 1).

Nous devons dire dès le début que nos recherches ont établi l'identité biologique de l'adrénaline efficiente (AE) et de la sympathine (SyE).

Tant l'AE que la SyE proviennent du CA et se retransforment en CA. L'AE et la SyE ont la même action sur les organes terminaux.

L'adrénaline se trouve sous deux formes dans l'organisme: L'adrénaline efficiente (AE) dans la capsule surrénale, qui est biologiquement identique à la sympathine efficiente (SyE) libérée par le neurone post-ganglionnaire sympathique (homologue de

la cellule chromaffine) dans tous les organes terminaux et le complexe adrénalinique (CA) ou préadrénaline.

L'AE est l'adrénaline que nous connaissons, excitatrice ou inhibitrice. Le CA entretient la réactivité des organes et sert de

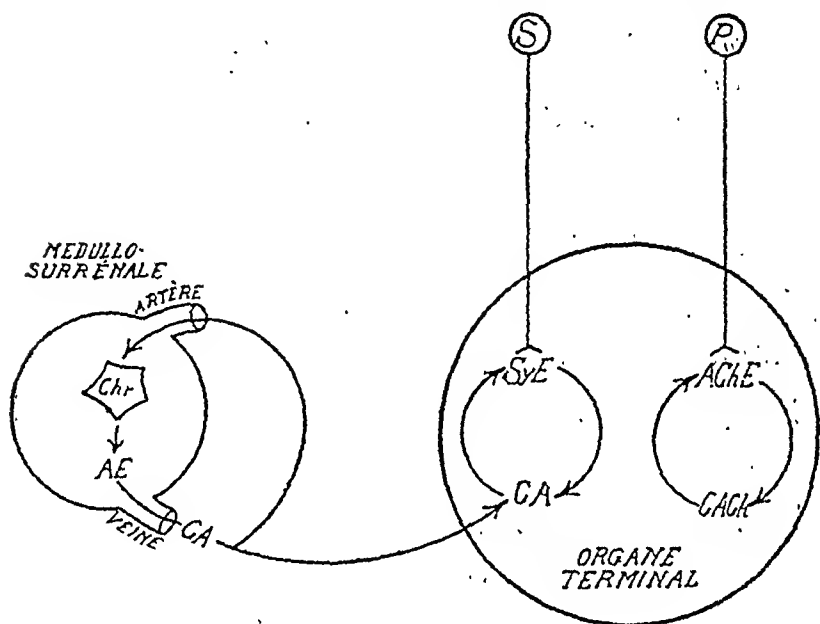


Fig. 1. — La cellule chromaffine (Chr) sécrète l'adrénaline efficiente (AE) laquelle se transforme, déjà dans le sang veineux, en complexe adrénalinique (CA) ou préadrénaline, dont la cellule chromaffine tire l'AE et le sympathique tire la sympathine efficiente (SyE).

L'organe terminal contient deux présubstances le complexe adrénalinique (CA) ou préadrénaline et le complexe acétylcholinique (CaCh) ou précholine. Du CA le sympathique tire la SyE et du CaCh le parasympathique tire l'acétylcholine efficiente (AChE).

La SyE se retransforme en CA et l'AChE en CACH.

AE → CA → AE

SyE → CA → SyE

AChE → CACH → AChE

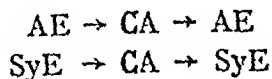
présubstance pour la formation de l'AE au niveau de la surrénale et de la SyE dans les organes terminaux.

L'AE et la SyE ne se trouvent, par conséquent, qu'au siège de leur production, alors que le CA se trouve tout dans le protoplasme cellulaire que dans les humeurs.

L'AE, dès qu'elle est déversée dans la veine cave inférieure, se transforme en CA, et c'est sous cette forme qu'elle arrive à l'organe terminal.

La SyE dès qu'elle agit se retransforme sur place en CA.

Ainsi donc:



Selon notre conception, il n'y a pas par conséquent, d'*adrénalinémie*. Il y a ce que nous avons appelé *préadrénalinémie*. L'AE et la SyE ont une action trop fugace pour que sous le rythme normal de leur production, elles se trouvent dans le sang sous la forme efficiente. Ce n'est que dans les états anormaux que l'adrénaline, formée en excès peut passer dans le sang et arriver jusqu'aux organes terminaux, produire une *adrénalinémie active*. Mais ces états sont tout à fait transitoires.

Quant à l'acétylcholine, voici son cycle d'évolution dans l'organisme, établi par nos recherches. L'acétylcholine efficiente (AChE) élaborée dans la cellule se transforme rapidement sur place en CACH. L'AChE est élaborée à partir du CACH et se retransforme en CACH.



Il n'y a pas d'*acétylcholinémie*. Il y a ce que nous avons appelé *précholinémie*. Le sang ne contient pas d'AE ou d'AChE qui aient une action excitatrice ou inhibitrice sur les organes terminaux. Il entretient seulement la réactivité des organes et leur fournit les pré-substances nécessaires (CA et CACH) à la formation de la SyE et de l'AChE.

Tout comme pour l'adrénaline et la sympathine, ce n'est qu'en cas de surproduction d'AChE, que cette substance, n'ayant pas le temps de se transformer en CACH, passe dans le sang sous la forme d'AChE. Ce n'est, en d'autres mots, qu'anormalement que nous rencontrons l'*acétylcholinémie*.

Cet état est transitoire, tout comme l'état adrénalinémique. L'*acétylcholinémie* très intense peut être mortelle.

B. *Le phénomène de l'acétylcholinogénèse et le phénomène de décho-linisation tissulaire. Facteurs acétylcholinergiques.*

Nous appelons *acétylcholinogénèse* le phénomène d'élaboration d'acétylcholine efficiente (AChE) à partir du complexe acétylcholinique (CACH).

Nous appelons *facteurs acétylcholinergiques* les facteurs qui libèrent de l'AChE à partir du CACH. Les facteurs acétylcholinergiques nerveux sont: le parasympathique et le neurone moteur périphérique dans l'organe terminal. Il s'élabore de même de l'acétylcholine au niveau des synapses. Nous avons démontré *qu'anormalement* de différents facteurs agissent sur la cellule et sans le concours de l'influx nerveux peuvent libérer de la sympathine et de l'acétylcholine. Tous ces facteurs sont aussi *acétylcholinergiques* et *sympathinergiques*. L'acétylcholine représente dans notre conception le facteur vital de première importance qui préside aux fonctions cellulaires, la sympathine étant produite pour limiter par son action antagoniste l'action de l'AChE.

Dans l'organe terminal, l'influx parasympathique dans l'organe végétatif, l'influx du neurone moteur périphérique et l'influx parasympathique dans le muscle volontaire, libèrent de l'AChE à partir du CACH: c'est le *phénomène d'acétylcholinogénèse*.

L'AChE étant libérée à partir du CACH, la concentration de ce dernier dans le protoplasme diminue.

Mais l'AChE, dès qu'elle agit, se retransforme en CACH et rétablit la concentration protoplasmique en cette substance. Cela concerne le protoplasme cellulaire dans l'organe terminal ou organe d'exécution (muscle strié ou lisse, glande, etc).

Dans la cellule nerveuse, qui envoie l'influx nerveux à l'organe terminal, se produit-il un phénomène analogue? Nous savons seulement que tout neurone élabore au bout de son axone de l'AChE. Tous les neurones, somatiques et végétatifs, élaborent de l'AChE, à l'exception du neurone post-ganglionnaire sympathique qui élabore de la SyE. Nous ne savons pas si elle est préformée dans la cellule nerveuse ou si l'influx nerveux émis par l'axone tire au niveau de synapse, à partir du CACH qui se trouve dans les humeurs, l'AChE. Nous inclinons beaucoup vers cette seconde hypothèse.

Quant aux humeurs nous admettons qu'elles contiennent le CACH.

La quantité d'AChE libérée dépend de l'intensité de l'influx et de la concentration en CACH des tissus.

Les états décrits par nous sous le nom d'*amphotonie* et d'*hypoamphotonie* sont représentés, le premier par une hyperconcentration, le second par une hypoconcentration des tissus et des humeurs en CACH et en CA. Dans l'amphotonie le même influx nerveux P libère plus d'AChE et le même influx nerveux S libère plus de SyE qu'à l'état normal.

Dans l'hypoamphotonie la libération des deux médiateurs chimiques est diminuée.

Dans ces deux formes de modifications du tonus végétatif, l'hyper- ou l'hypoproduction de SyE et d'AChE n'est pas due seulement à l'hyper- ou à l'hypoconcentration en CA et en CACH, mais aussi à un tonus plus élevé du S et du P. Par le phénomène décrit par nous sous le nom de *mécanisme circulaire amphotrope* une hyper- ou une hypoactivité d'un organe augmente ou diminue, d'une manière réflexe le tonus des centres végétatifs S et P, ce qui augmente ou diminue l'intensité de l'influx S et P.

Ainsi donc, dans l'amphotonie l'acétylcholinogénèse est augmentée, et dans l'hypoamphotonie, elle est diminuée. Comme il y a en même temps *hyper-* ou *hyposympathinogénèse* l'équilibre se maintient. Mais souvent un phénomène prédomine de beaucoup sur l'autre.

Une excitation du parasympathique (excitation du vague) ou une excitation réflexe à prédominance parasympathique (excitation du bout central du déresseur ou du sinus carotidien) déclenche surtout une hyperacétylcholinogénèse.

De même, une excitation du sympathique ou une excitation réflexe à prédominance sympathique déclenche surtout une hypersympathinogénèse.

Il est admis que l'AChE et la SyE ne peuvent être libérés que par l'influx nerveux. Nous avons démontré que cette conception est erronée. De différents facteurs physiques, chimiques, etc. qui agissent sur l'organe terminal sont capables de déclencher la production d'AChE et de SyE. Il y a toujours prédominance d'un médiateur sur l'autre.

L'ésérine, la pilocarpine, la muscarine, en dehors d'autres actions, libèrent, selon nous, la SyE du CA et l'AChE du CACH, mais surtout l'AChE. La digitale et la strophantine libèrent du

s'ensuit une décholinisation tissulaire et une hypovagotonie, qui explique d'ailleurs la tachycardie fébrile.

D'autres facteurs acétylcholinergiques lorsqu'ils agissent d'une manière intense, appauvrissent les tissus en précholine et pendant un certain temps, même plusieurs jours, la concentration en précholine diminue.

L'expérience suivante le prouve. La dose de 2 cm³ d'une suspension de gélose injectée dans la veine provoque chez le cobaye neuf de 300 g un choc acétylcholinique mortel. Mais si nous injectons la dose de $\frac{1}{4}$ —1 cm³ de gélose et le lendemain la dose de 2 cm³, cette dose n'est plus mortelle. Le phénomène s'explique par la décholinisation tissulaire qu'a provoqué la première injection. Les tissus se sont appauvris en précholine et la deuxième injection a libéré moins d'acétylcholine. Nous avons démontré que ce qu'on a appelé anti-anaphylaxie n'est en grande partie due qu'à un phénomène de décholinisation tissulaire.

C. Nouvelle conception sur l'action des substances étrangères introduites dans l'organisme.

Chaque substance étrangère possède son action propre et agit différemment sur l'organe terminal. Mais il existe un groupe de substances étrangères dont l'action ressemble d'une manière frappante à l'action des médiateurs chimiques, tout en étant tout à fait différente au point de vue de leur constitution chimique. C'est que ces substances agissent par l'intermédiaire des médiateurs chimiques. Ces substances, du moins d'après ce que nous ont montré nos recherches, semblent être très nombreuses. Si pour certaines d'entre elles, on a vaguement reconnu l'intervention des médiateurs chimiques, les effets de beaucoup d'autres sont considérés comme des effets directs, sans aucune intervention des médiateurs.

Les effets de la muscariné ressemblent beaucoup à ceux de l'acétylcholine; les effets de la digitale ressemblent, en ce qui concerne l'excitabilité, la tonicité, et la contractilité à ceux de la sympathine et en ce qui concerne l'automaticité et la conductibilité à ceux de l'acétylcholine; l'éphédrine a une action analogue à celle de l'adrénaline; de différentes substances irritantes du tissu conjonctif cutané ont une action semblable à celle de l'histamine; l'injec-

s'ensuit une décholinisation tissulaire et une hypovagotonie, qui explique d'ailleurs la tachycardie fébrile.

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L'expérience suivante le prouve. La dose de 2 cm³ d'une suspension de gélose injectée dans la veine provoque chez le cobaye neuf de 300 g un choc acétylcholinique mortel. Mais si nous injectons la dose de $\frac{1}{4}$ —1 cm³ de gélose et le lendemain la dose de 2 cm³, cette dose n'est plus mortelle. Le phénomène s'explique par la décholinisation tissulaire qu'a provoqué la première injection. Les tissus se sont appauvris en précholine et la deuxième injection a libéré moins d'acétylcholine. Nous avons démontré que ce qu'on a appelé anti-anaphylaxie n'est en grande partie due qu'à un phénomène de décholinisation tissulaire.

C. Nouvelle conception sur l'action des substances étrangères introduites dans l'organisme.

Chaque substance étrangère possède son action propre et agit différemment sur l'organe terminal. Mais il existe un groupe de substances étrangères dont l'action ressemble d'une manière frappante à l'action des médiateurs chimiques, tout en étant tout à fait différente au point de vue de leur constitution chimique. C'est que ces substances agissent par l'intermédiaire des médiateurs chimiques. Ces substances, du moins d'après ce que nous ont montré nos recherches, semblent être très nombreuses. Si pour certaines d'entre elles, on a vaguement reconnu l'intervention des médiateurs chimiques, les effets de beaucoup d'autres sont considérés comme des effets directs, sans aucune intervention des médiateurs.

Les effets de la muscariné ressemblent beaucoup à ceux de l'acétylcholine; les effets de la digitale ressemblent, en ce qui concerne l'excitabilité, la tonicité, et la contractilité à ceux de la sympathine et en ce qui concerne l'automaticité et la conductibilité à ceux de l'acétylcholine; l'éphédrine a une action analogue à celle de l'adrénaline; de différentes substances irritantes du tissu conjonctif cutané ont une action semblable à celle de l'histamine; l'injec-



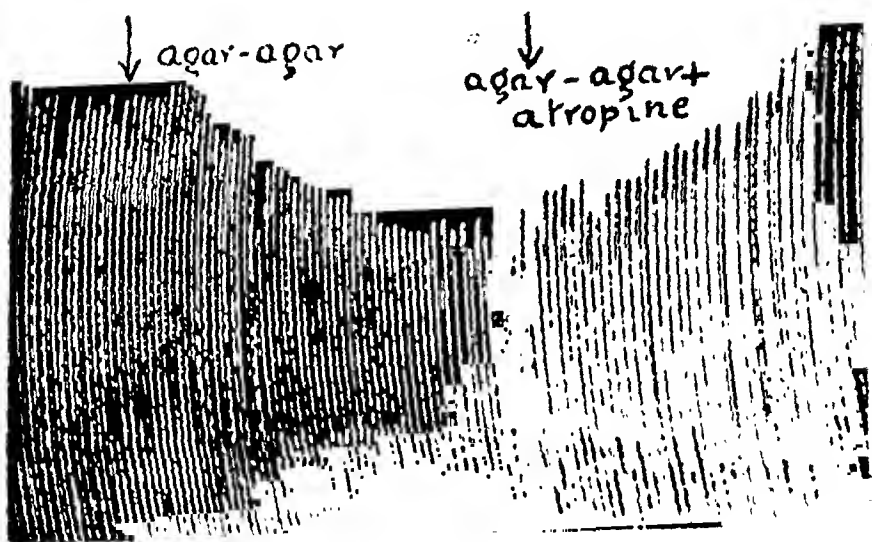


Fig. 3 — Action acétylcholinergique d'une suspension d'agar-agar dans l'eau physiologique sur le cœur isolé de grenouille. Action empêchante de l'atropine. Nous avons préparé la suspension d'agar-agar à chaud dans l'eau physiologique à 1/400. Après refroidissement nous diluons à 1/1000. La perfusion du cœur de grenouille avec cette suspension à 1/1000 produit un effet semblable à celui de l'acétylcholine. Nous ajoutons de l'atropine au liquide de perfusion; l'action inhibitrice disparaît.

tion intraveineuse d'un sérum étranger produit des effets semblables à ceux provoqués par l'acétylcholine; l'injection de sérum de cheval produit des effets acétylcholiniques. Il en est de même de plusieurs autres antigènes (extraits bactériens, etc).

Bordet a soutenu qu'une suspension de gélose injectée dans la veine libère l'anaphylatoxine et provoque un choc anaphylactique. Nous avons démontré qu'en réalité la gélose libère de l'acétylcholine, phénomène qui n'a rien à faire avec l'anaphylaxie (fig. 2, 3, 4).

Les traités classiques affirment que les médicaments agissent directement sur l'organe terminal ou sur les nerfs: la muscarine agirait sur les terminaisons parasympathiques, l'adrénaline sur les terminaisons sympathiques, la digitale sur les fibres myocardiques et les terminaisons nerveuses, un sérum étranger aurait une action directe sur la cellule, etc. En réalité ils agissent sur la cellule de l'organe terminal.

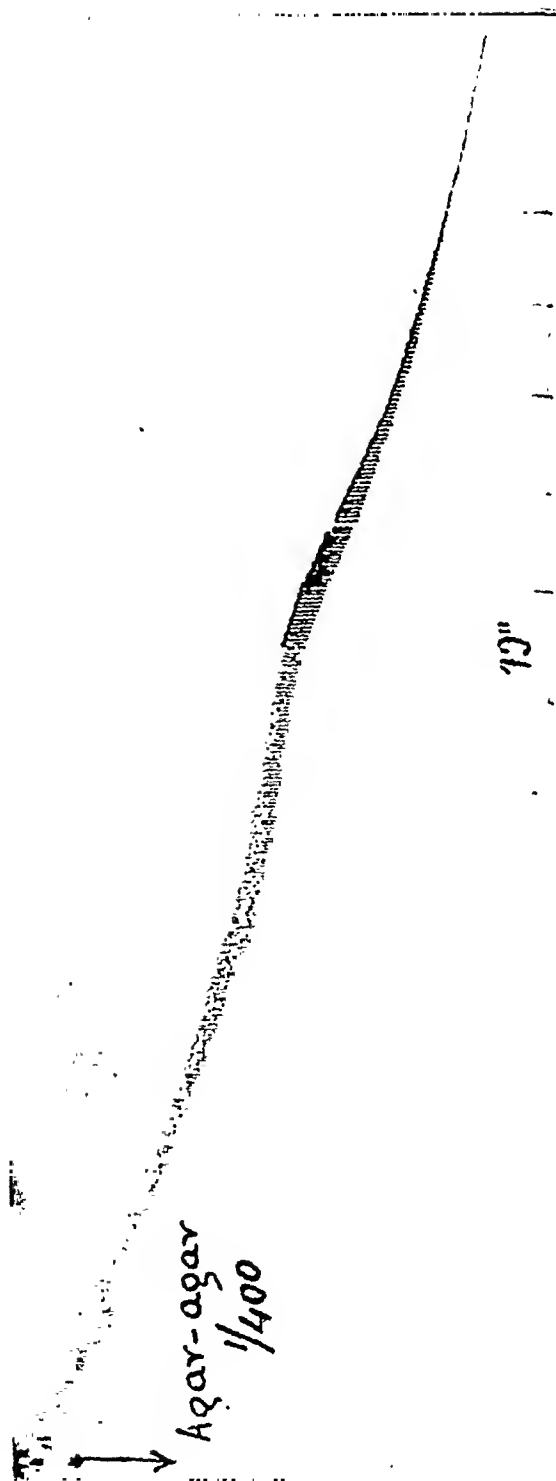


Fig. 4. — Choc acétyleholinique mortel provoqué par une injection intra-veineuse d'agar-agar sur la pression sanguine. Chat 2100 g. Anesthésié au Dial. 1. Injection intra-veineuse de 1 cm³ d'une suspension d'agar-agar dans l'eau physiologique (préparée à chaud selon la formule de Bordet) en dilution de 1/100 provoque un choc acétyleholinique mortel.

Peut-on s'imaginer qu'une substance qui agit sur la cellule terminale (laquelle contient dans son protoplasme les présubstances dont normalement les nerfs végétatifs tirent les médiateurs chimiques) ne trouble en rien la formation de ces médiateurs? Et lors qu'on constate que certaines substances produisent des effets ressemblant à ceux des médiateurs chimiques, ne sommes-nous autorisés à supposer qu'elles agissent par ces médiateurs? Il nous semble que dans l'action des substances étrangères, nous devons étudier les relations qui pourraient exister entre les effets produits, les médiateurs chimiques, les ions et tous les autres facteurs qui interviennent dans le fonctionnement normal des organes.

Nous ne nous occuperons ici que des substances étrangères dont l'action semble s'exercer par les médiateurs chimiques.

Il est classique d'admettre que les médiateurs chimiques (acétylcholine et sympathine) ne peuvent être libérés que par l'influx nerveux. C'est là une grande erreur. Nos recherches ont démontré que les médiateurs chimiques peuvent être libérés par des substances étrangères, indépendamment de toute intervention de l'influx nerveux.

Toute une série de substances étrangères introduites dans l'organisme ont deux actions: une action spécifique et une action non spécifique.

L'action non spécifique peut s'exercer de plusieurs manières:

a) Libération de médiateurs chimiques (ésérine, pilocarpine, petites doses d'atropine, digitale, strophantine, etc).

b) Action sur le cycle d'évolution des médiateurs chimiques. L'ésérine empêche l'inactivation de l'AChE qui s'accumule dans les tissus.

c) Action empêchante sur l'effet de la SyE (action sympathofrénatrice: ergotamin 883 F, 933 F) ou de l'AChE (action parasympathofrénatrice d'une dose moyenne d'atropine, ou sur l'effet des deux (action amphofrénatrice: grandes doses d'atropine, de 883 F, de 933 etc).

L'action est toujours double (amphomimétique ou amphofrénatrice), mais prédomine plus dans un sens ou dans l'autre.

Il s'ensuit une modification dans l'équilibre fonctionnel de l'organe.

L'action spécifique est différente suivant la substance employée. Par cette action la substance tend à modifier le protoplasme cellulaire pouvant provoquer des altérations irréversibles.

Contre cette action la cellule réagit par une riposte, que nous appelons *riposte cellulaire défensive*. Il s'agit de la production de ferments, d'anticorps ou d'autres moyens de défense qui tendent à débarrasser l'organisme de la substance étrangère introduite.

Parmi les substances étrangères qui libèrent de l'AChE nous citons les antigènes. Comme nous l'avons dit dans le 1-er mémoire, les antigènes ont une action non spécifique (action acétylcholinergique) et une action spécifique.

D. Action acétylcholinergique des antigènes.

Dans nos recherches expérimentales faites sur les vaisseaux du chat et du chien, ainsi que sur le coeur isolé de grenouille, nous avons démontré que les antigènes libèrent de l'acétylcholine. Nous l'avons

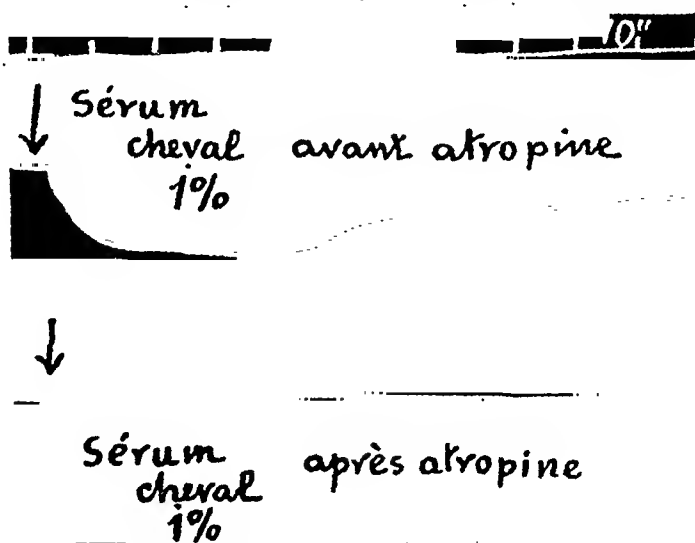


Fig. 5. — Chien. Action acétylcholinique du sérum de cheval injecté dans l'artère sur les vaisseaux de la patte du chien.

Technique. Nous inserivons dans le bout périphérique de l'artère fémorale (sectionnée) la pression récurrente. Nous plaçons une canule dans le bout central de l'artère fémorale pourvue d'un tube de caoutchouc fermé à l'aide d'une pince à son bout. A travers le tube de caoutchouc nous injectons le sérum de cheval. La substance injectée passe à travers les anastomoses qui relient le bout central avec le bout périphérique de l'artère fémorale dans les vaisseaux de la patte sur lesquelles elle agit. Toute vasoconstriction fait monter la pression récurrente et toute vasodilatation la fait baisser.

Le sérum de cheval produit une vasodilatation (par libération d'acétylcholine) qui ne se produit plus après l'atropine.

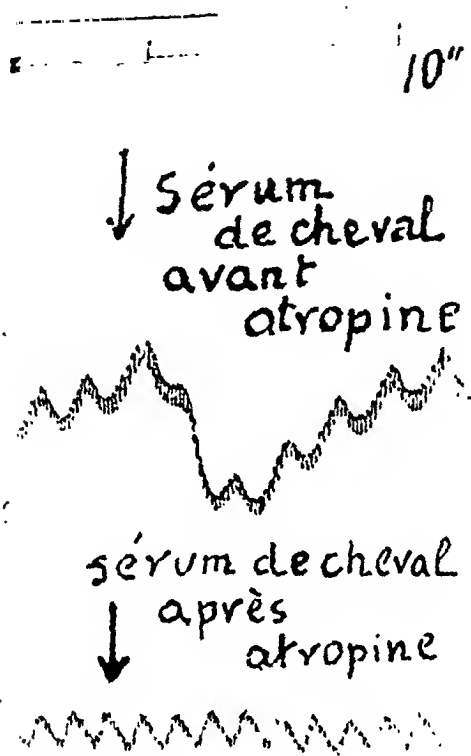


Fig. 6. — Le sérum de cheval injecté dans la veine chez le chat libère de l'acétylcholine qui provoque une hypotension. L'hypotension ne se produit plus si nous injectons préalablement de l'atropine qui empêche l'action de l'acétylcholine.

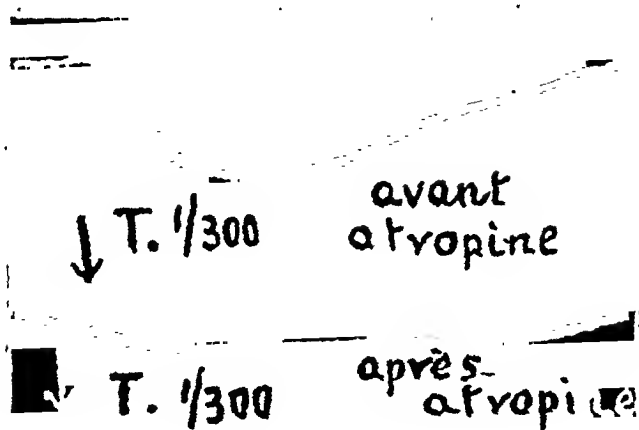


Fig. 7. — La tuberculine libère de l'acétylcholine et produit une vasodilatation. Son action est empêchée par l'atropine (recherches sur les vaisseaux de la patte du chien. — technique indiquée dans la légende de la fig. 5).

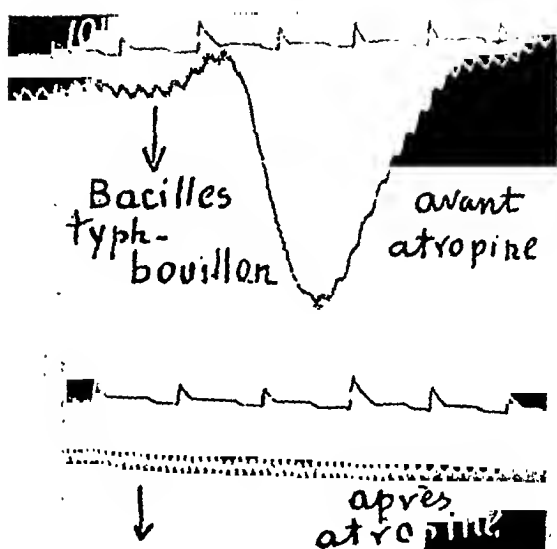


Fig. 8. — Une émulsion de bacilles typhiques (culture sur gélose) non débarrassés par le lavage à l'eau physiologique de ses produits solubles libère de l'acétylcholine et provoque une vasodilatation, phénomène qui ne se produit plus après l'atropine.

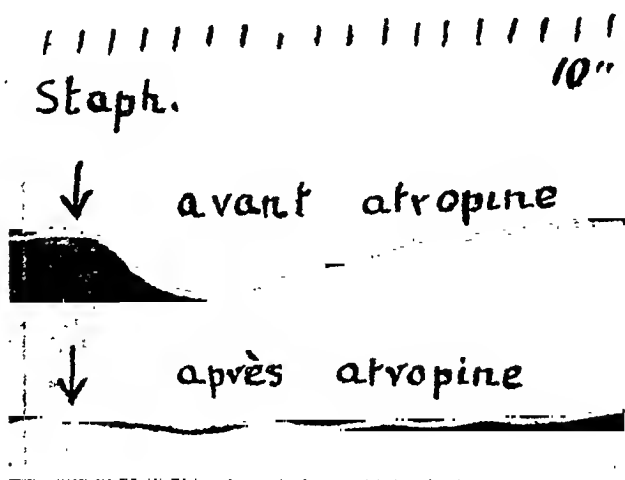


Fig. 9. — Émulsion d'une culture sur gélose de staphylocoques lavés à l'eau physiologique et maintenus pendant quelques heures dans l'eau distillée à 37°. Nous ajoutons ensuite la quantité de NaCl nécessaire pour rendre le liquide isotonique. Cette émulsion injectée dans l'artère fémorale (technique indiquée dans la légende de la fig. 5) provoque une vasodilatation (action acétylcholinergique). La même émulsion ne produit plus le phénomène après l'atropine, substance qui empêche l'action de l'acétylcholine.

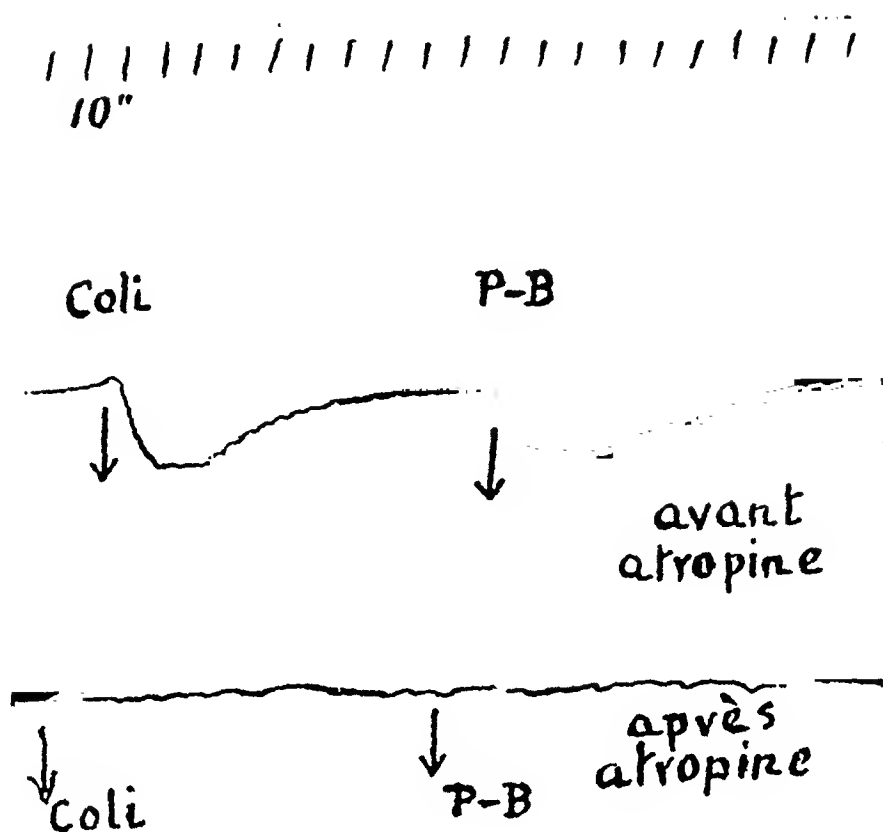


Fig. 10. — Une émulsion de colibacilles ou de paratyphique B préparée selon la technique indiquée dans la légende de la fig. 5 produit sur les vaisseaux de la patte du chien une vasodilatation (action acétylcholinergique). La même émulsion ne produit plus le phénomène après l'atropine, substance qui empêche l'action de l'acétylcholine.

prouvé pour le sérum étranger (fig. 5—6), pour la tuberculine (fig. 7), pour les produits bactériens (fig. 8, 9, 10). Ces substances injectées dans la veine libèrent de l'acétylcholine. La nature acétylcholinique des phénomènes obtenus est démontrée par le fait qu'ils sont exagérés par l'ésérine et empêchés par l'atropine.

Chez l'homme une première injection de sérum étranger provoque un choc qui, lorsque l'injection est faite dans la veine, peut être mortel. On a parlé de *toxicité propre du sérum* (explication qui ne veut rien dire). On a supposé qu'il s'agit dans ces cas de sujets s'étant antérieurement nourris de viande de cheval et que les phénomènes produits sont dus à ce qu'on appelle anaphylaxie. Il n'en est rien —: le choc ainsi produit n'a rien à faire avec l'im-

munité. Il s'agit d'un choc acétylcholinique pur, dû à l'action non spécifique acétylcholinergique de l'antigène.

Il est à remarquer que nous n'avons pas obtenu le phénomène d'acétylcholinogénèse avec des bactéries soigneusement débarrassées par des lavages répétés à l'eau physiologique de leurs produits de sécretion. Par contre nous l'avons obtenu avec des bactéries non débarrassées de leurs produits ou maintenues pendant quelques heures à 37° dans l'eau distillée.

Nous considérons l'antigène bactérien, non pas la bactérie elle-même, mais ses produits d'élaboration. Ce sont ces produits qui provoquent la libération d'acétylcholine. Nous considérons le phénomène de l'acétylcholinogénèse comme la première réaction de l'organisme vis-à-vis d'un antigène.

Un antigène introduit dans l'organisme peut ne produire aucune réaction. Dans ce cas il ne s'adapte pas à l'organisme, dans lequel il circule comme un simple corps étranger et finit par être éliminé d'une manière ou d'une autre sans provoquer ni phénomène d'immunité, ni paraphylaxie, ni maladie spécifique. Et le premier phénomène qui se produit et qui est indispensable pour que l'antigène s'adapte à l'organisme et provoque des réactions de la part de ce dernier, est l'acétylcholinogénèse.

E. Action acétylcholinergique de l'acide *P*-aminobenzoïque.

Nous savons que l'acide *p*-aminobenzoïque joue un rôle très important dans la vie et la multiplication des microbes et qu'il faut lui accorder un rôle primordial dans la production des infections. Or, nos recherches démontrent que l'acide *p*-aminobenzoïque a une action acétylcholinergique.

Dans notre Institut A. Rudeanu a démontré sur le coeur isolé de grenouille que l'acide *p*-aminobenzoïque a une action inhibitrice.

Nos recherches faites chez le chat, la pression générale et sur les vaisseaux de la patte du chien ont démontré que l'acide *p*-aminobenzoïque libère de l'acétylcholine (fig. 11—15). En effet, son action est intensifiée par l'ésérine qui favorise l'intervention de l'acétylcholine et empêchée par l'atropine qui empêche l'action de cette dernière substance.

Nous attribuons à l'acétylcholine un rôle vital de première importance. Elle joue un rôle de premier ordre dans tous les phéno-

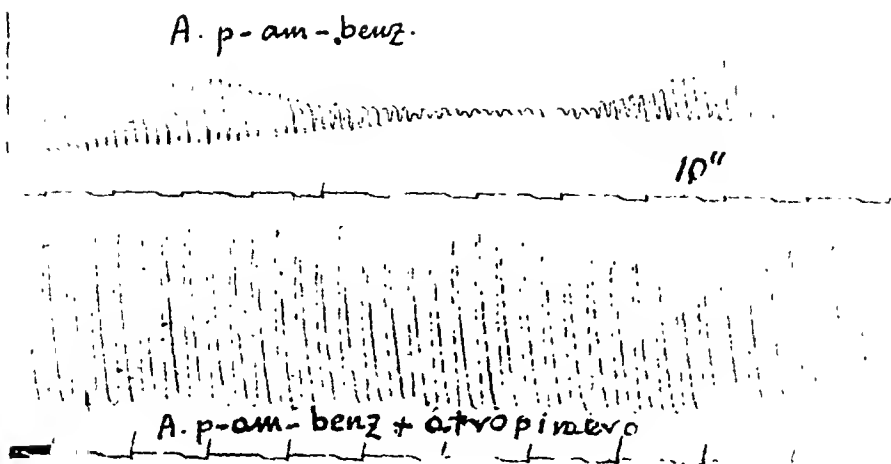


Fig. 11. — L'acide p-aminobenzoïque est acétylcholinergique. Sur le cœur isolé de grenouille il produit une inhibition qui ne se produit plus en présence de l'atropine qui empêche l'action de l'acétylcholine

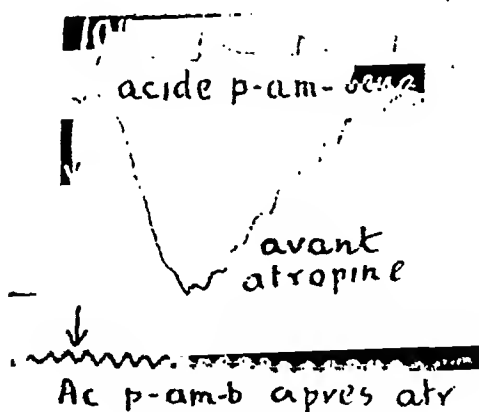


Fig. 12 — En injection intra-veineuse chez le chat l'acide p-aminobenzoïque produit une hypotension par libération d'acétylcholine. L'acide p-a-b ne produit plus le phénomène d'hypotension après préparation de l'animal à l'atropine qui empêche l'action de l'acétylcholine.

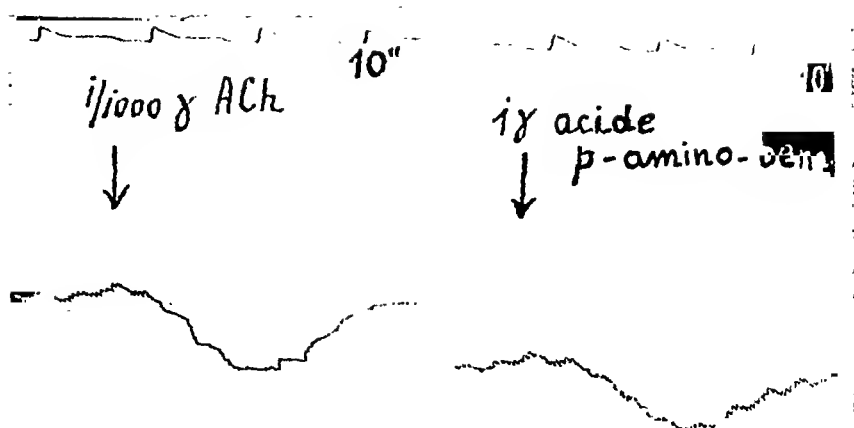


Fig. 13. — Action vasodilatatrice comparative sur la pression sanguine de l'acide p-aminobenzoïque et de l'acétylcholine (injection intra-veineuse chez le chat). L'action est identique. 1 γ d'acide p-aminobenzoïque provoque un effet égal à celui produit par 1/1000 γ d'acétylcholine.

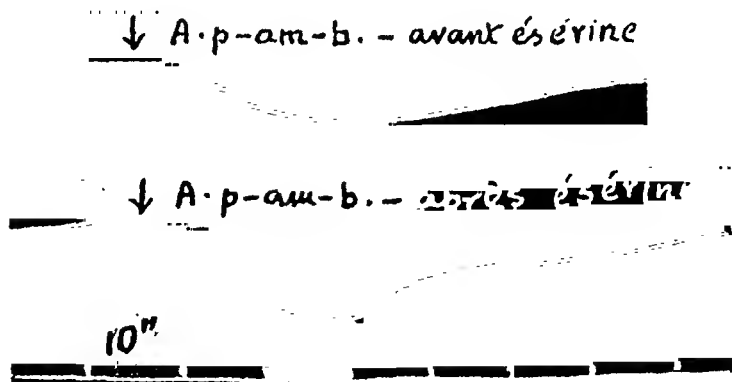


Fig. 14. — Action acétylcholinergique de l'acide p-aminobenzoïque sur les vaisseaux de la patte du chien (technique indiquée dans la légende de la figure 5). L'a p-a-b produit une vasodilatation, phénomène qui est exagéré par l'éserine, ce qui démontre qu'il est produit par la libération d'acétylcholine.

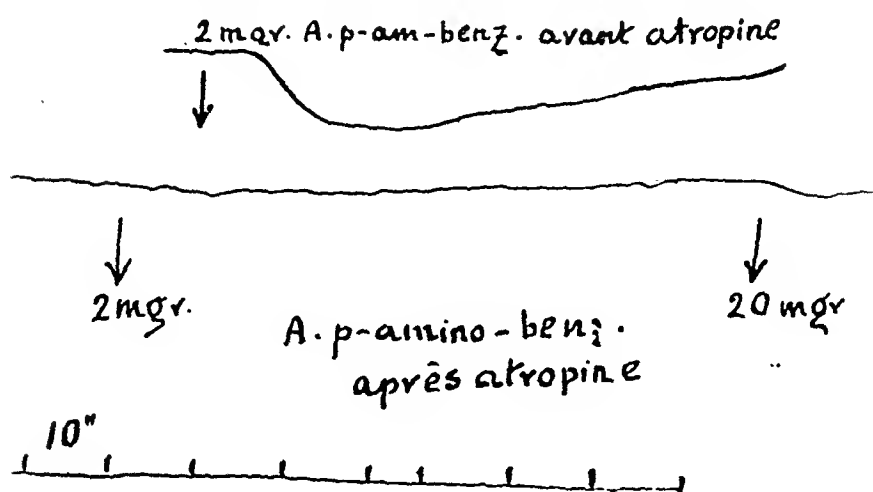


Fig. 15. — Action acétylcholinergique de l'acide p-aminobenzoïque sur les vaisseaux de la patte du chien. Action vasodilatatrice qui ne se produit plus après l'anatropine, ce qui démontre que le phénomène se produit par libération d'acétylcholine. (Technique indiquée dans la légende de la fig. 5).

mènes vitaux de l'organisme, entre autres dans la formation des anticorps.

L'action acétylcholinergique de l'acide p-aminobenzoïque nous conduit à croire que dans son action sur le métabolisme et le développement des microbes cette substance agit, (en partie du moins) par son action acétylcholinergique et d'un autre côté que l'acide p-aminobenzoïque joue un certain rôle par cette dernière action dans la formation des anticorps.

(De l'Institut Clinico-Médical A de l'Hôpital Filantropia (1-ère Clinique médicale de l'Université de Bucarest) Directeur: Prof. D. Danielopolu.

Recherches sur le mécanisme de l'immunité, de l'anaphylaxie et des maladies spécifiques (maladie du sérum, maladies infectieuses).

Phylaxie, paraphylaxie et choc paraphylactique acétylcholinique.

3-ème Mémoire.

Preuves et arguments en faveur de notre hypothèse.

Par

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(Ce travail est parvenu à la rédaction le 3 Février 1944).

Nous avons énuméré dans le premier mémoire les objections que nous avons à formuler contre la conception classique. Nous exposerons maintenant les preuves et les arguments qui viennent à l'appui de notre hypothèse.

A. Action acétylcholinergique des antigènes et de l'acide P-aminobenzoïque.

Nous avons traité cette question dans le 2-ème mémoire. Nous avons démontré que le premier phénomène qui se produit lors de l'introduction de l'antigène dans l'organisme est l'acétylcholinogénèse. La production d'acétylcholine est indispensable à l'adaptation de l'antigène à l'organisme, ainsi qu'à la production des anticorps et de la maladie spécifique.

B. *Ce qu'on appelle choc anaphylactique est choc paraphylactique acétylcholinique.*

Nous prouvons que:

1°. le choc dit anaphylactique est un choc acétylcholinique.

2°. le choc n'est pas un phénomène d'hypersensibilité, opposé à l'immunité; mais un phénomène produit à côté de l'immunité, dont il dépend très étroitement et dont il représente simplement un *déchet*.

1° — *Le choc dit anaphylactique est de nature acétylcholinique.*

a) Les phénomènes qui apparaissent pendant le choc ressemblent à ceux que produit l'acétylcholine: inhibition cardiaque, hypotension, bronchoconstriction, hypermotilité digestive, vésicale et utérine, convulsions, hypocoagulabilité du sang, leucopénie avec mononucléose et éosinophilie.

Nous avons reproduit ces phénomènes par une injection intra-veineuse d'acétylcholine.

Pendant le choc dit anaphylactique toutes les propriétés fondamentales du myocarde diminuent, tout comme après l'acétylcholine. L'électrocardiogramme montre un ralentissement du rythme et un blocage auriculo-ventriculaire dans les deux cas. L'effet bathmo- tono-inotrope négatif est plus difficile à constater, mais est certain.

Nous obtenons les mêmes effets avec l'ésérine, qui agit en facilitant l'intervention de l'acétylcholine. La digitale et la strophanthine agissent sur le tissu embryonnaire du myocarde (noeud sino-auriculaire et faisceau de His) en libérant surtout de l'acétylcholine: ces substances produisent un effet chrono-dromotrope négatif, tout comme dans le choc paraphylactique ¹.

L'hypotension du choc est identique à celle produite par l'acétylcholine. Elle est favorisée par l'ésérine qui favorise l'intervention de l'acétylcholine et empêchée par l'atropine qui empêche l'intervention de cette dernière. Il en est de même de l'hypermotilité digestive, vésicale et utérine.

Dans les convulsions qui apparaissent pendant le choc, l'acétylcholine joue un rôle essentiel. Nous les avons reproduites par l'acé-

¹ Nous avons démontré que ces médicaments libèrent plus d'acétylcholine que de sympathine dans le tissu embryonnaire du coeur (action chrono-dromotrope négative) et plus de sympathine que d'acétylcholine dans le tissu myocardique adulte (action bathmo-ino-tonotrope positive).

tylcholine et par l'ésérine. L'atropine les empêche. Le neurone moteur périphérique libère de l'acétylcholine qui est un des facteurs essentiels du tonus musculaire. L'acétylcholine libérée augmente le tonus, phénomène qui est à la base des convulsions.

La bronchoconstriction est aussi un phénomène acétylcholinique. L'ésérine, la pilocarpine, l'excitation du vague, qui agissent tous par l'acétylcholine provoquent une bronchoconstriction. Elle est empêchée par l'atropine. Nous avons provoqué l'asthme expérimental chez le cobaye et le lapin par une injection intra-trachéale d'acétylcholine.

Disons enfin que l'acétylcholine, à une certaine dose, provoque une hypocoagulation du sang, une leucopénie, avec mononucléose et éosinophilie, phénomènes que nous rencontrons aussi dans le choc.

Pendant le choc l'acétylcholine est libérée dans tous les organes qui sont le siège de formation des anticorps-choline. Tous les tissus innervés par le système végétatif produisent ces anticorps, mais les uns plus que les autres. Le tissu réticulo-endothélial est un siège important de production des anticorps. Or, ce tissu possède une riche innervation végétative. Les cellules nerveuses sont selon nous aussi le siège de production des anticorps. Nous croyons pouvoir affirmer que tous les organes terminaux qui contiennent la présubstance dont est libérée l'acétylcholine (préchole) et les cellules nerveuses qui libèrent aussi de l'acétylcholine sont le siège de production des anticorps.

Nous connaissons le mouvement de rotation du cobaye pendant le choc acétylcholinique. Nous l'avons reproduit chez le cobaye neuf par une injection intra-cérébrale faite latéralement à 5 mm de profondeur, au niveau des centres coordinateurs de la musculature volontaire.

Nous attirons l'attention sur le fait que le choc acétylcholinique provoqué chez un cobaye par une injection intra-veineuse d'acétylcholine n'est pas tout à fait identique au choc dit anaphylactique. Lorsque le choc est provoqué par une injection intra-veineuse d'acétylcholine, cette substance est apportée par le sang, alors que dans le choc elle naît sur place, dans l'intimité de la cellule où se trouve l'anticorps-choline et où se forme le complexe antigène-anticorps-alexine. Or, la formation des anticorps-choline dans les tissus ne se fait pas avec la même intensité dans tous les

tissus et il est logique d'admettre que l'acétylcholinogénèse sera d'autant plus intense dans un tissu, que ce dernier contient plus d'anticorps. Et la formation des anticorps-choline dépend de la concentration en précholine des tissus, qui est aussi inégale.

C'est de cette manière que nous expliquons certains phénomènes localisés plus accentués dans le choc paraphylactique, comme par exemple le mouvement de rotation, n'apparaissant pas après une injection intra-veineuse d'acétylcholine. Ce mouvement dénote la libération locale d'une forte quantité d'acétylcholine dans les centres coordinateurs de la musculature volontaire.

Quant à l'action de l'atropine qui empêche tant le choc produit par une injection intraveineuse d'acétylcholine que le choc paraphylactique, elle s'explique par le fait que cette substance modifie la cellule de l'organe terminal qui perd sa réactivité à l'acétylcholine. Il est naturel que le choc acétylcholinique, tout en étant plus ou moins différent dans les deux expériences, soit empêché par l'atropine.

b) Nous avons démontré que l'agar-agar en suspension dans l'eau physiologique (préparé suivant la formule de Bordet) injecté dans la veine provoque un choc acétylcholinique. La symptomatologie du choc produit par l'agar-agar est identique à celle du choc dit anaphylactique, ce qui démontre la nature acétylcholinique de ce dernier. Cette identité de symptomatologie a conduit Bordet à affirmer que le choc gélosique est un choc anaphylactique provoqué par l'anaphylatoxine que la gélose libérerait à partir de l'alexine par un phénomène d'adsorption. En réalité, le choc gélosique n'a rien à faire avec l'anaphylaxie. Il est un choc acétylcholinique non paraphylactique dû à l'action acétylcholinergique de la gélose. Si la symptomatologie est identique à celle du choc paraphylactique c'est parce que les deux se produisent par l'acétylcholine. En plus, tant le choc provoqué par l'agar-agar que le choc dit anaphylactique, est exagéré par l'ésérine (qui favorise l'action de l'acétylcholine, et empêchée par l'atropine (qui empêche l'action de l'acétylcholine).

c) Nous avons démontré que tous les antigènes sont acétylcholinergiques. Avec une forte dose de sérum étranger introduit dans la veine nous provoquons chez le cobaye neuf un choc acétylcholinique qui ressemble à celui provoqué par une très petite dose de sérum injecté dans la veine chez un cobaye préalablement traité

avec le même sérum (et par conséquent en état de paraphylaxie). Dans les deux cas il s'agit d'un choc acétylcholinique. Dans le premier cas il n'est pas paraphylactique, dans le second, il est paraphylactique. Dans les deux cas le choc est favorisé par l'ésérine et empêché par l'atropine. Sympatomatologiquement ils se ressemblent parce qu'en dernière analyse c'est l'acétylcholine qui produit le choc. Mais dans le premier cas il faut une forte dose de sérum, dans le second une très petite dose est suffisante pour provoquer le choc.

Nous examinerons cette différence de plus près. Lorsque nous injectons à un sujet neuf un sérum étranger ce dernier agit par son action non spécifique acétylcholinergique en libérant de l'acétylcholine à partir de la précholine. Cette dernière se trouve dans les tissus en concentration normale. Lorsque nous injectons le sérum à un sujet immunisé contre ce sérum et en état de paraphylaxie la libération d'acétylcholine se fait à l'occasion de la formation du complexe phylactique, dans un organisme en état d'hyperconcentration tissulaire en précholine. Une trace de l'antigène est suffisante pour provoquer le complexe phylactique et l'acétylcholine est libérée à partir de la précholine qui se trouve en excès.

d) La symptomatologie du choc paraphylactique est identique, n'importe quel serait l'antigène qui a provoqué la paraphylaxie et ressemble au choc provoqué par l'acétylcholine. Or, l'immunité à côté de laquelle s'établit la paraphylaxie est spécifique. Si l'anaphylaxie était aussi spécifique, la symptomatologie du choc varierait selon l'antigène qui est en cause.

e) Tous les facteurs qui favorisent l'intervention de l'acétylcholine favorisent aussi le choc paraphylactique acétylcholinique et tous les facteurs qui empêchent l'intervention de l'acétylcholine empêchent aussi le choc.

Les expériences faites à ce sujet jusqu'à nos recherches sont arrivées à des conclusions contradictoires. John Auer a signalé en 1910 le fait que l'atropine empêche la bronchoconstriction qui apparaît pendant le choc et qui serait, d'après tous les auteurs, la cause de la mort. Zunz a obtenu des résultats semblables. Mais Mita, Schmidt et Hape n'ont rien obtenu. D'autres auteurs ont favorisé le choc avec l'ésérine ou la pilocarpine, mais Levy Solal et Franck ont empêché par contre le choc par la pilocarpine. L'adrénaline empêcherait le choc. Pasteur Valéry Radot, Hagenau et

Dolfuss ont soutenu qu'il n'y a aucune relation entre le système nerveux de la vie végétative et le choc dit anaphylactique.

Nous expliquons ces résultats contradictoires par le fait que les auteurs n'ont pas tenu compte de l'amphomimétisme de l'ésérine, de la pilocarpine et de l'adrénaline, de l'action inverse des petites et des grandes doses de ces substances, du fait que les petites doses d'atropine sont amphomimétiques et les doses supérieures parasymphathofrénatrices, enfin du fait que chez le lapin il existe un ferment qui inactive l'atropine en la dédoublant en tropine et acide tropique.

Voici, en résumé, les résultats de nos recherches en ce qui concerne l'action pharmacodynamique de ces substances.

Il est erroné de croire que l'adrénaline est sympathomimétique et l'acétylcholine est parasymphathomimétique. Les deux substances agissent dans les deux sens, phénomène que nous avons appelé amphomimétisme. L'adrénaline provoque dans la cellule de l'organe terminal un phénomène s-mimétique (réponse cellulaire) qui déclenche de la part de la cellule un phénomène parasymphathomimétique (riposte cellulaire compensatrice), qui se produit par libération d'acétylcholine et qui tend à rétablir l'équilibre; l'acétylcholine provoque un phénomène parasymphathomimétique (réponse cellulaire) lequel déclenche de la part de la cellule un phénomène s-mimétique (riposte cellulaire compensatrice) qui se produit par libération de sympathine et qui tend à rétablir l'équilibre. Nous appelons encore la réponse cellulaire *action directe* et la riposte cellulaire compensatrice *action indirecte*. Dans nos recherches la sympathine s'est montrée biologiquement identique à l'adrénaline.

La sympathine libérée par le sympathique provoque une réponse cellulaire, laquelle déclenche une riposte cellulaire compensatrice par libération d'acétylcholine; l'acétylcholine libérée par le parasymphathique provoque une réponse cellulaire laquelle déclenche une riposte cellulaire compensatrice par libération de sympathine. Il est par conséquent erroné de croire qu le S et le P agissent d'une manière tout à fait indépendante dans l'organe terminal. Chacun provoque une réponse, laquelle déclenche une riposte cellulaire compensatrice qui tend à rétablir l'équilibre fonctionnel de l'organe. C'est ce que nous avons appelé *mécanisme inter-symphatho-parasymphathique de l'organe terminal*.

L'amphomimétisme pour les facteurs naturels est ce que nous avons appelé *amphomimétisme subséquent*: la riposte est, subséquente à la réponse cellulaire.

Nous avons démontré d'un autre côté que l'ésérine et la pilocarpine sont amphomimétiques. L'ésérine empêche l'action de la cholinestérase et favorise de cette manière l'action de l'acétylcholine qu'elle intensifie et prolonge. Mais nos recherches ont démontré que l'ésérine possède encore l'action de libérer de l'acétylcholine et de la sympathine. A petite dose elle libère plus d'acétylcholine que de sympathine (action amphomimétique à prédominance parasympathique amph-P) et à grande dose elle libère plus de sympathine que d'acétylcholine (action amphomimétique à prédominance sympathique amph. S). Par le même mécanisme la pilocarpine s'est montrée dans nos recherches à petite dose amph P et à grande dose amph S.

Nos recherches ont démontré que le Calcium est amph P à petite dose et amph S à grande dose. Nous appelons l'action amphomimétique de ces substances étrangères *amphomimétisme simultané* car il est le résultat de la libération simultanée de sympathine et d'acétylcholine.

Les recherches que nous avons poursuivies sur l'atropine nous ont démontré que —:

— à petite dose l'atropine libère plus d'acétylcholine que de sympathine. Elle est amph P,

— à dose plus grande elle empêche l'action de l'acétylcholine, effet que nous avons appelé *action parasympathofrénatrice*

— à très grande dose elle empêche tant l'action de l'acétylcholine que celle de la sympathine, effet que nous avons appelé *action amphofrénatrice*.

Aucun des auteurs qui ont travaillé avant nous sur l'action de l'adrénaline, de l'ésérine de la pilocarpine et de l'atropine sur l'anaphylaxie et l'immunité n'ont pas tenu compte de ces faits résultant de nos recherches et qui se confirment tous les jours. Et c'est pour ces raisons que les résultats de ces auteurs sont contradictoires.

Il suffit qu'un auteur emploie une petite dose d'adrénaline et un autre une grande dose, pour que le premier obtienne une facilitation du choc et le second un empêchement. Il en est de même pour le Ca, et les autres substances amphomimétiques.

Les erreurs faites avec l'atropine sont les plus graves. Il suffit qu'un auteur emploie une petite dose d'atropine qui libère de l'acétylcholine et un autre une dose supérieure qui empêche l'action de l'acétylcholine, pour que le premier obtienne une facilitation et le second un empêchement du choc. A cela s'ajoute un fait très important lorsqu'on travaille sur le lapin. Le lapin possède dans ses tissus un ferment qui inactive l'atropine en la dédoublant en tropine et acide tropique. Il faut alors *injecter dans la veine* une dose énorme d'atropine pour obtenir un effet parasymphathofréateur.

Dans les recherches que nous avons faites en 1908—1910 nous avons obtenu aussi des résultats très surprenants avec l'atropine et l'adrénaline, parce que nous ne connaissions pas exactement l'action de ces substances et nous nous servions de doses trop petites. Ce n'est qu'après de longues études sur le Système nerveux de la vie végétative — que nous avons poursuivies pendant plus de 30 ans — et surtout après avoir travaillé dans la question des médiateurs chimiques, que nous avons pu établir les doses à employer et les principes d'interprétation des résultats obtenus.

Employées d'une manière logique ces substances nous ont permis d'arriver à la conclusion suivante:

Tout facteur qui facilite l'intervention de l'acétylcholine favorise le choc et tout facteur qui empêche l'intervention de l'acétylcholine empêche aussi le choc.

Nous résumerons plus bas très succinctement les résultats de nos recherches faites sur environ 500 animaux (cobayes et lapins).

— *Esérine*. Nous avons choisi une dose d'esérine qui facilite suffisamment l'intervention de l'acétylcholine. Pour provoquer le choc nous nous servons d'un mélange d'antigène-anticorps (généralement hématies de mouton + sérum de lapin anti-mouton) que nous injectons dans la veine chez le cobaye neuf.

Nous dosons la dose minime de ce mélange qui provoque un choc classique. Une dose de ce mélange qui chez le cobaye non ésérinisé ne produit rien, provoque un choc classique la plupart du temps mortel chez le cobaye ésérinisé.

— *Adrenaline*. Nous avons obtenu en général avec une petite dose d'adrénaline une facilitation du choc et avec une grande dose un empêchement. Mais les résultats ne sont pas toujours très nets, fait que nous expliquons par l'amphomimétisme de l'adréna-

line. Cette substance provoque un phénomène s-mimétique qui déclenche un phénomène p-mimétique qui se produit par libération d'acétylcholine. Nous avons là par conséquent à compter avec deux facteurs: un facteur s-mimétique qui empêche le choc et un facteur p-mimétique qui le favorise.

— *Adrénaline après ergotamine.*

L'ergotamine empêche l'action s-mimétique de l'adrénaline, qui devient exclusivement p-mimétique. En réalité l'adrénaline après l'ergotamine agit exclusivement par l'acétylcholine qui est libérée pendant la riposte cellulaire compensatrice.

Nous préparons les cobayes neufs d'abord à l'ergotamine et ensuite à l'adrénaline qui, par la riposte cellulaire compensatrice qu'elle produit libère de l'acétylcholine. Chez un cobaye ainsi préparé une dose d'antigène-anticorps incapable de provoquer le choc chez un cobaye témoin (non préparé à l'ergotamine-adrénaline) donne un choc classique mortel.

— *Strophantine.*

Nous avons démontré que la digitale et la strophantine agissent par la libération de médiateurs chimiques; qu'elles libèrent dans le tissu myocardique adulte plus de sympathine que d'acétylcholine et dans le tissu embryonnaire (noeud sinoauriculaire et faisceau de His) plus d'acétylcholine que de sympathine.

C'est de cette manière que nous avons expliqué le fait, curieux en apparence, que la même substance produise un effet positif sur certaines propriétés myocardiques (action bathmo-ino-tonotrope positive) et négatif sur d'autres (action chrono-dromotrope négative). C'est que l'excitabilité, la tonicité et la contractilité du cœur, sont des propriétés de la fibre myocardique adulte, alors que l'automatisme et la conductibilité a—v sont des propriétés de la fibre embryonnaire. Or, dans la fibre adulte la digitale et la strophantine libèrent plus de sympathine dont l'action est positive et dans la fibre embryonnaire elles libèrent plus d'acétylcholine dont l'action est négative. L'électrocardiogramme montre que pendant le choc paraphylactique acétylcholinique le cœur s'arrête par action chrono- et dromotrope négative (ralentissement normotope et bloc a—v), phénomène que nous attribuons à l'acétylcholine.

Or, dans nos recherches la strophantine qui agit de la même manière sur l'automatisme et sur la conductibilité, favorise énormément le choc paraphylactique acétylcholinique. Le cobaye

strophantinisé fait un choc avec une dose d'antigène-anticorps beaucoup plus petite que le cobaye non strophantinisé. Cette action favorable est due à l'action libératrice d'acétylcholine dans le tissu embryonnaire du coeur de la strophantine.

— *Atropine.*

Dans nos recherches l'atropine à petite dose a favorisé légèrement le choc dans quelquesunes de nos expériences. Son action favorisante est très légère, car ces doses libèrent peu d'acétylcholine.

A doses parasympathofrénatrices l'atropine empêche dans 100 % des expériences le choc paraphylactique acétylcholinique. Le cobaye atropinisé résiste à des doses d'antigène-anticorps trois et quatre fois plus grandes que la dose qui produit le choc classique mortel chez le témoin non tropinisé.

— *Esérine-atropine et strophantine-atropine.*

Nous avons démontré que l'ésérine et la strophantine favorisent le choc par le fait que ces substances favorisent l'intervention de l'acétylcholine.

Nous avons fait l'expérience de contrôle suivante.

Un premier lot de cobayes est préparé à l'ésérine; un second lot à la strophantine; un troisième lot est préparé à l'ésérine et ensuite à l'atropine; un quatrième lot est préparé à la strophantine et ensuite à l'atropine; un cinquième lot de cobayes ne reçoit aucune préparation.

Les cobayes du 1-er et du 2-ème lots font le choc après des doses d'antigène-anticorps qui chez les cobayes du 5-ème lot ne produisent rien.

Les cobayes du 3-ème et du 4-ème lots ne font pas de choc même avec des doses d'antigène — anticorps 3 et 4 fois plus fortes que celles qui provoquent le choc chez les cobayes du 5-ème lot. —

f) L'atropine empêche et l'ésérine favorise le choc provoqué par une injection intraveineuse d'acétylcholine et le choc gélosique qui est aussi un choc acétylcholinique.

Nos expériences ont été faites sur le lapin et le cobaye. L'acétylcholine injectée dans la veine provoque un choc acétylcholinique. Ce choc est un peu différent du choc paraphylactique acétylcholinique par le fait que le choc produit par l'injection intra-veineuse d'acétylcholine est dû à l'action de l'acétylcholine distribuée d'une manière égale pour la circulation aux organes, alors que dans le choc

paraphylactique acétylcholinique l'acétylcholine est libérée sur place, dans la cellule. Or, chez l'animal immunisé contre un antigène la concentration en anticorps et par conséquent en précholeline n'est pas la même dans tous les organes. Les tissus capables de fabriquer plus d'anticorps présentent aussi une concentration en précholeline plus élevée. Aussi, pendant le choc, ce sont ces tissus qui sont le siège le plus intense de l'acétylcholinogénèse et dont le tonus est par conséquent modifié le plus dans le sens parasympathique.

Tout naturellement l'atropine par son action empêchante sur l'acétylcholine empêche tant le choc provoqué expérimentalement par l'injection intra-veineuse d'acétylcholine que le choc paraphylactique acétylcholinique. Ce fait démontre une fois de plus que ce dernier choc est de nature acétylcholinique.

L'atropine empêche aussi le choc gélosique, que nous avons démontré être de nature acétylcholinique. La gélose, par un trouble colloïdal provoqué sur la cellule libre de l'acétylcholine, dont l'atropine empêche l'action.

Dans nos expériences l'éserine favorise le choc provoqué par une injection intraveineuse d'acétylcholine ou de gélose.

Après l'éserine nous pouvons provoquer chez le lapin et chez le cobaye un choc acétylcholinique mortel avec une dose d'acétylcholine ou de gélose beaucoup plus petite que la dose minime qui provoque le choc mortel chez le témoin non préparé à l'éserine.

g) Nous avons démontré en 1931 que l'accès d'asthme se produit par libération d'acétylcholine, et cela tant dans l'asthme dit anaphylactique (que nous appelons asthme paraphylactique) que dans l'asthme provoqué par un facteur nerveux (émotion, réflexe, etc).

Or, nous constatons que l'accès d'asthme paraphylactique a une symptomatologie identique n'importe quel serait l'antigène qui a provoqué la paraphylaxie locale. Nous constatons de même que la symptomatologie de l'asthme paraphylactique est identique à celle de l'asthme non paraphylactique, produit par un facteur nerveux (émotion, réflexe). Or, l'asthme nerveux se produit par la libération d'acétylcholine, ce qui démontre une fois de plus que le choc paraphylactique est acétylcholinique. Dans le choc général il s'agit d'un état de phylaxie et paraphylaxie général et de libération générale d'acétylcholine pendant le choc; dans l'asthme il s'agit

d'un état de phylaxie et paraphylaxie locale et de libération bronchique locale (ou surtout locale) d'acétylcholine.

Nous reviendrons en détail sur la question dans un paragraphe ultérieur.

h) Nous avons décrit en 1922 deux états végétatifs anormaux: l'amphotonie caractérisée par un état d'hyperconcentration des tissus en précholine et l'hypoamphotonie caractérisée par un état d'hypoconcentration des tissus en ces deux présubstances.

L'amphotonie et l'hypoamphotonie peuvent être constitutionnelles ou acquises. Parmi les amphotonies acquises nous signalons l'hyperthyroïdisme, que nous avons démontré ne pas être une sympathicotonie, mais une amphotonie à prédominance sur le groupe exciteur. Parmi les hypoamphotonies acquises nous avons décrit l'hypoamphytonie qui se rencontre pendant les infections ou chez les cachectiques, chez les débiles.

Or, nous constatons que, grâce à l'hyperconcentration en précholine des tissus l'amphotonie constitutionnelle et l'amphotonie basédovienne favorisent le choc général ou local (accès d'asthme), alors que l'hypoamphotonie constitutionnelle et l'hypoamphotonie des maladies infectieuses aiguës ou cachectiques empêchent le choc. Ce qu'on appelle *anergie* n'est d'après nous qu'un état d'hypoamphotonie due à une hypoconcentration des tissus en précholine.

i) Nous avons trouvé dans nos recherches que les complexes phylactiques formés avec les anticorps qui agissent avec le concours de l'alexine libèrent rapidement une grande quantité d'acétylcholine au moment de leur formation (*acétylcholinogénèse explosive*) et que les complexes phylactiques formés avec des anticorps qui agissent sans alexine libèrent l'acétylcholine plus lentement (*acétylcholinogénèse lente*).

Or, l'acétylcholine, dès qu'elle est libérée s'inactive et il faut qu'une grande quantité d'acétylcholine soit libérée à la fois pour que le choc paraphylactique acétylcholinique apparaisse. Voilà pourquoi ce n'est qu'avec les complexes phylactiques à acétylcholinogénèse explosive que le choc est évident. Mais si nous préparons l'animal à l'ésérine, nous obtenons un choc paraphylactique acétylcholinique net même avec les complexes phylactiques sans alexine. Nos expériences ont été faites chez le cobaye avec le mélange neutre de toxine — antitoxine diphtérique. Le mélange employé par nous, injecté dans la veine, chez le cobaye neuf, même

à grande dose, ne provoquait aucun choc. La libération d'acétylcholine se faisant d'une manière lente, elle s'inactive rapidement et le choc n'est pas évident.

Après ésérinisation de l'animal, le même mélange provoquait un choc paraphylactique acétylcholinique classique. L'ésérine empêche l'inactivation de l'acétylcholine et en même temps libère cette substance: le choc devient évident. En tout, elle favorise l'intervention de l'acétylcholine.

2° — *Le choc dit anaphylactique ne signifie nullement une sensibilisation de l'organisme.* — Il s'agit d'un phénomène produit à côté de l'immunité et dépendant de ce dernier phénomène. C'est un phénomène paraphylactique, déchet du phénomène d'immunité.

Un cobaye injecté avec du sérum de cheval, n'est pas sensibilisé mais immunisé contre ce sérum. Lorsque nous faisons la deuxième injection l'antigène nouvellement introduit forme avec l'anticorps un complexe immunisant (et non pas sensibilisant), qui libère de l'acétylcholine. Il en est de même dans ce qu'on appelle anaphylaxie passive et anaphylaxie in vitro: il s'agit de phénomène d'immunité passive in vitro, phénomènes accompagnés de libération d'acétylcholine, qui provoque le choc paraphylactique métylcholinique, qui libère de l'acétylcholine, qui déclenche le choc.

Si le choc était l'expression d'une hypersensibilité de l'organisme vis-à-vis de telle ou telle substance, il faudrait que le choc présente pour chaque substance une symptomatologie à part. Or, la symptomatologie est toujours identique, ou du moins contient des symptômes identiques.

Si l'immunité et l'anaphylaxie étaient deux états indépendants et opposés les facteurs qui favorisent un état devraient empêcher l'autre et inversement. Or, nous avons démontré que tous les facteurs qui favorisent l'immunité favorisent aussi l'anaphylaxie et tous les facteurs qui empêchent l'immunité empêchent aussi l'anaphylaxie.

Salomonsen et Madsen, Stella Litarczck, Bellak, Saghy et Czeresznyes, Nordicko et beaucoup d'autres auteurs ont trouvé que la pilocarpine et l'ésérine favorisent la production des anticorps et que l'atropine l'empêche. Nous expliquons l'action favorisante de l'ésérine sur la production des antigènes par la libération d'acétylcholine et son action empêchante sur la cholinesthère et l'action

empêchante de l'atropine par son action empêchante sur l'acétylcholine. Or, nous démontrons que tous les anticorps sont immunisants et qu'il n'existe pas d'anticorps anaphylactisants. Et d'un autre côté la pilocarpine et l'ésérine favorisent le choc et l'atropine l'empêche. Ainsi donc, tous les facteurs qui favorisent l'immunité favorisent aussi ce qu'on appelle anaphylaxie et tous les facteurs qui empêchent l'immunité empêchent aussi ces deux états.

Il est très naturel d'ailleurs que la paraphylaxie soit favorisée par les mêmes facteurs que la phylaxie, car elle n'est qu'une dépendance de cette dernière.

Les anticorps ne peuvent se produire qu'en étroite union avec l'acétylcholine. Au fur et à mesure de leur production la concentration en précholine des tissus augmente, ce qui constitue l'état de paraphylaxie.

Disons encore que l'amphotonie qui favorise la paraphylaxie, favorise aussi l'immunité et que l'hypoamphotonie empêche les deux états.

Les hyperthyroïdiens s'immunisent plus facilement et font des phénomènes paraphylactiques plus intenses; les cachectiques (qui sont hypoamphotoniques) s'immunisent difficilement et ne font pas de phénomènes paraphylactiques.

C. L'état de paraphylaxie est un état d'hyperconcentration des tissus en précholine.

L'antigène libre de l'acétylcholine et provoque l'apparition des anticorps qui se forment en étroite union avec la précholine tissulaire. A mesure que les anticorps se forment, la concentration en précholine des tissus augmente.

Nous avons démontré que chaque fois qu'un facteur végétatif augmente d'intensité, le facteur antagoniste tend à contrebalancer son action en augmentant aussi son action. — L'hyperproduction d'acétylcholine est accompagnée d'une hyperproduction de sympathine. C'est pour cette raison que les états de sympathicotonie et de vagotonie sont exceptionnels et que presque toujours il se produit une amphotonie, c'est à dire un état d'hyperconcentration tissulaire tant en précholine qu'en préadrénaline.

A l'état d'amphotonie s'oppose ce que nous avons appelé l'hypoamphotonie, état dans lequel la concentration des tissus en préadrénaline et en précholine est diminuée.

Nous avons décrit l'amphotonie et l'hypoamphotonie constitutionnelle et l'amphotonie et l'hypoamphotonie acquises. L'amphotonie provoquée par un antigène, que nous appelons amphotonie paraphylactique, est une amphotonie acquise. Dans l'amphotonie paraphylactique c'est surtout l'hyperconcentration en précholine qui est exagérée.

Nous avons dit que tout antigène provoque cet état de phylaxie — paraphylaxie. Si la phylaxie est complète, tout l'antigène est fixé et rendu inoffensif et la maladie spécifique ne se produit plus. Si la phylaxie est incomplète il apparaît après une certaine période d'incubation la maladie spécifique correspondante. Que l'immunité soit complète ou qu'elle soit incomplète, il se produit à côté l'état de paraphylaxie.

Ainsi donc, l'incubation de la maladie spécifique (maladie du sérum, maladies infectieuses, etc) est caractérisée par une hyperconcentration tissulaire en précholine.

Nous prouvons l'état d'hyperconcentration en précholine des tissus pendant la paraphylaxie par les faits suivants:

a) Chez l'homme, pendant l'incubation de la maladie du sérum la réaction à l'adrénaline est identique à celle qui se produit lorsque les tissus présentent une hyperconcentration en précholine.

La même dose, qui chez le sujet normal a une action amphomimétique à prédominance sympathique (amph S) produisant une élévation de la pression sanguine et une accélération du cœur, devient isomimétique (action nulle) ou même amphomimétique à prédominance parasympathique, produisant de la bradycardie et une hypotension (amph P). Voici le mécanisme du phénomène. Nous avons démontré que l'adrénaline n'est pas sympathomimétique mais amphomimétique; qu'à petite dose elle est amph P et à grande dose elle est amph S; qu'entre les petites et les grandes doses se trouve une dose intermédiaire dont l'action s-mimétique et p-mimétique sont égales (action nulle ou presque nulle) et que nous avons appelée *isomimétique*. L'adrénaline provoque un phénomène s-mimétique que nous appelons *réponse cellulaire*, laquelle déclenche dans la cellule un phénomène parasympathomimétique

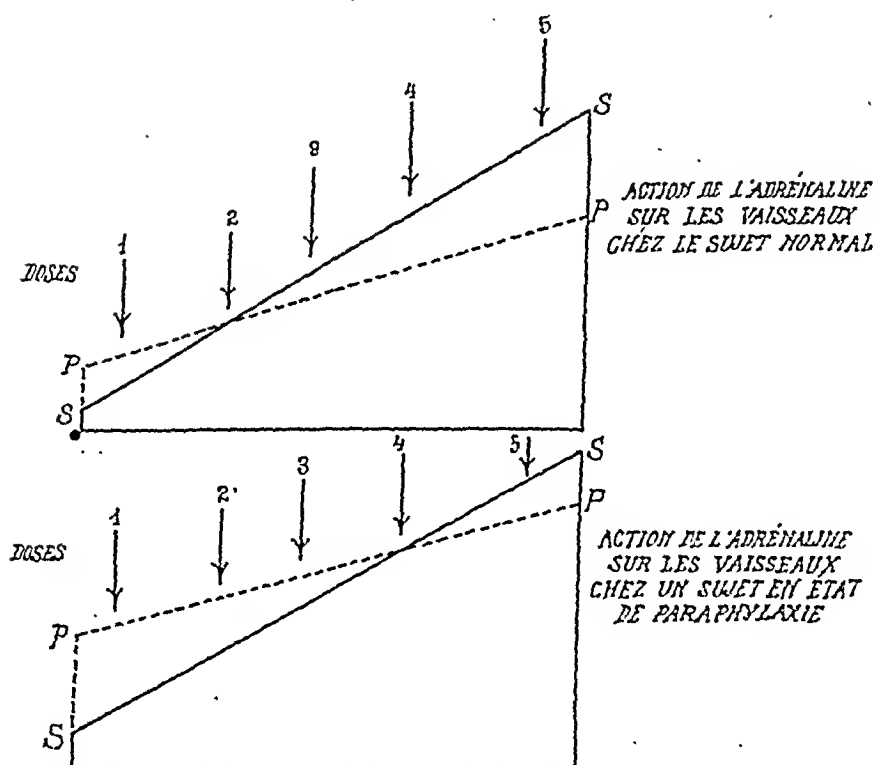


Fig. 1 — Action amphomimétique de l'adrénaline sur les vaisseaux normaux et sur les vaisseaux dans un organisme en état de paraphylaxie.

Doses 1, 2, 3, 4, 5. — Doses de plus en plus grandes d'adrénaline.

Normal. L'adrénaline a une action S-mim. Elle produit sur les vaisseaux de la circulation générale une réponse cellulaire qui est S-mim, laquelle déclenche la libération d'AChE qui provoque la riposte cellulaire compensatrice qui est p-mim.

Petites doses (amph P): action S-mim. < action p-mim = vasodilatation.

Grandes doses (amph S): action P-mim < action s-mim = vasoconstriction.

Doses isomimétiques: action S-mim. = action P. mim.

Paraphylaxie. La riposte prend naissance par libération d'AChE à partir du CACH (préchochine). Plus la concentration des tissus immunisés en préchochine est élevée, plus la quantité d'AChE libérée sera grande.

A mesure que la concentration en anticorps-choline monte, la source dont est libérée l'AChE est plus riche.

La dose 1 (amph P) vasodilatatrice normalement, produit une vasodilatation plus forte dans la paraphylaxie.

La dose 2 normalement isomimétique est amph P dans la paraphylaxie (action vasodilatatrice).

La dose 3 encore plus grande, normalement amph S et par conséquent vasoconstrictrice est amph P et par conséquent vasodilatatrice dans la paraphylaxie.

La dose 4 normalement amph S (vasoconstrictrice) est isomimétique (pas d'action) dans la paraphylaxie.

La dose S (vasoconstrictrice) tant normalement que dans la paraphylaxie aura un effet vasoconstricteur moins intense dans ce dernier état que sur des vaisseaux normaux.

C'est de cette manière que nous avons expliqué en 1922 et 1923 la réaction spéciale à l'adrénaline dans certains états végétatifs anormaux.

C'est de cette manière que nous expliquons le fait qu'une dose vasoconstrictrice d'adrénaline a un effet moins vasoconstricteur, on n'a aucun effet ou a un effet vasodilatateur dans les états de paraphylaxie.

Ce sont ces raisons qui nous ont conduit à la conclusion thérapeutique suivante. Le traitement à l'adrénaline dans le choc dit anaphylactique est contre-indiqué, parce que dangereux. Il est formellement interdit d'employer l'adrénaline non précédée d'atropine, qui empêche l'action de l'acétylcholine, substance qui se dégage pendant la riposte.

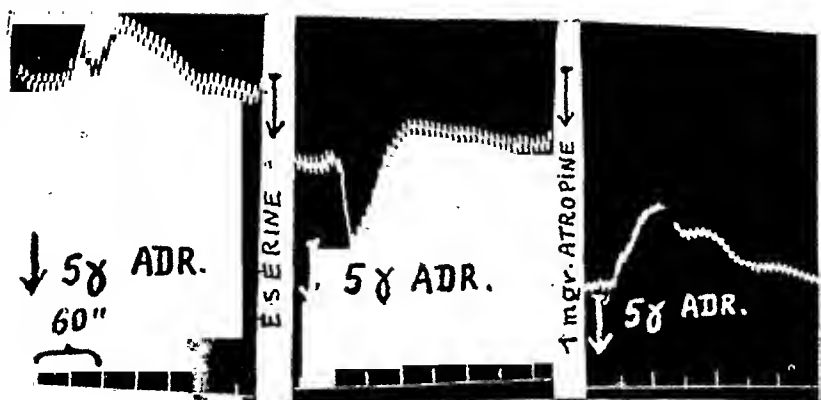


Fig. 2. — Chat, la dose de 5 γ est amph S et produit une vasoconstriction. L'adrénaline provoque par son action directe S-mim une réponse cellulaire qui déclenche une *riposte cellulaire compensatrice* qui se produit par libération d'AChE. La réponse s-mim. est plus intense que la riposte p-mim. (action amph S). Après l'ésérine la quantité d'ACh libérée qui produit la riposte cellulaire compensatrice est plus grande; d où riposte > réponse: action amph. P (vasodilatation). Après atropine l'action P. mim. disparaît et la même dose d'adrénaline produit une vasoconstriction (action excl. S-mim.). La vasoconstriction est plus intense qu'avant l'atropine.

Cette expérience démontre que l'action P-mim. de l'adrénaline se fait par libération d'AChE. Selon nos recherches l'ésérine possède, en dehors de son action empêchante sur la cholinestérase une véritable action libératrice de médiateurs chimiques et surtout d'AChE.

que nous appelons *riposte cellulaire compensatrice* et qui se produit par libération d'acétylcholine.

La riposte cellulaire compensatrice est par conséquent un phénomène de réaction cellulaire qui tend à rétablir l'équilibre dérangé par l'action s-mimétique de l'adrénaline. Et l'acétylcholine libérée pendant la riposte provient de la précholine. Plus la concentration des tissus en précholine sera élevée plus la riposte compensatrice cellulaire sera intense. Avec une petite dose la prédominance parasympathique sera dans ces cas plus forte, une dose isomimétique deviendra amph P, une dose amph S deviendra isomimétique ou même amph P (fig. 1.).

La réaction à l'adrénaline telle qu'elle se produit pendant l'incubation de la maladie du sérum prouve un état d'hyperconcentration des tissus en précholine. Et comme cette dernière se produit comme corollaire de l'état de phylaxie, l'hyperconcentration en précholine des tissus est un signe de formation d'anticorps choline.

Chez une malade qui avait reçu plusieurs années auparavant une injection de sérum anti-diphthérique on pratique une injection de sérum anti-tétanique. Pour éviter les accidents paraphylactiques on lui injecte sous la peau un mg d'adrénaline, dose qui chez le sujet normal provoque une accélération du rythme et une hypotension. Immédiatement après elle fait une forte bradycardie et un état de collapsus avec forte hypotension. La dose d'un mg d'adrénaline qui chez le sujet normal est amph S, a en chez cette malade une action amph P, grâce à l'état d'hyperconcentration des tissus en précholine.

Nous avons pu expérimentalement transformer l'action amph S en action amph P en traitant préalablement l'animal par l'ésérine qui facilite l'action de l'acétylcholine. Dans l'expérience de la fig. 2 une dose d'adrénaline amph S qui produit une vasoconstriction devient amph P après l'ésérine. Cette transformation est le résultat de l'acétylcholine libérée pendant la riposte cellulaire compensatrice, car après l'atropine la même dose d'adrénaline produit de nouveau une vasoconstriction et même une vasoconstriction plus intense qu'avant l'atropine.

b) Nous avons démontré que l'atropine à petite dose libère de la sympathine et surtout de l'acétylcholine (action amph P) et à dose plus grande elle empêche l'action de l'acétylcholine (action parasympathofrénatrice). La limite entre la dose amph P et l'action p-frénatrice est naturellement située d'autant plus haut que la concentration en précholine est plus élevée. En effet, la quantité d'acétylcholine libérée est d'autant plus élevée que la concentration en précholine des tissus est plus grande.

Nous trouvons qu'une dose qui est déjà p-frén. chez le sujet normal est encore amph P pendant l'incubation de la maladie du sérum, ce qui prouve un état d'hyperconcentration en précholine.

c) Dans l'asthme la réaction des bronches à l'adrénaline et à l'atropine démontre l'hyperconcentration *locale* en précholine. Une dose amph S d'adrénaline qui dilate les bronches peut devenir amph P et provoquer une bronchoconstriction; une dose p-frén. d'atropine qui dilate les bronches peut exagérer le bronchospasme devenant amph P. Nous avons constaté ces phénomènes dans plusieurs cas d'asthme très intenses que nous avons eu à soigner. Nous reviendrons sur cette question dans un paragraphe à part.

En général l'atropine (par son action parasympathofrénatrice) et l'adrénaline (par son action amph S) produisent une broncho-dilatation. Mais lorsque l'état d'hyperconcentration en précho-line des tissus bronchiques est très élevée, l'atropine peut avoir une action amph P et l'adrénaline une action amph P et provoquer une bronchoconstriction.

d) On a prétendu que pendant l'état appelé anaphylaxie l'excitabilité des nerfs est augmentée. Voici ce qui se passe en réalité. L'excitation du vague produit sur le coeur des effets inhibiteurs plus intenses que chez l'animal normal. Mais cela ne veut pas dire que l'excitabilité des filets parasympathiques du vague est augmentée. Les tissus étant pendant l'incubation en hyperconcentration acétylcholinique l'excitation des filets parasympathiques produit un effet plus intense, car la source dont provient l'acétylcholine est plus élevée.

D. — L'état de paraphylaxie n'est pas spécifique. Elle est identique, n'importe quel antigène serait en cause et consiste toujours en une hyperconcentration en précholine.

Selon la conception classique l'anaphylaxie est spécifique, étant due à des anticorps spécifiques. Nous soutenons que la paraphylaxie n'est pas spécifique, mais qu'elle est liée à l'immunité qui — elle — est spécifique. L'antigène provoque un état d'immunité spécifique, par la formation d'anticorps spécifiques. Mais ces anticorps se forment en étroite union avec la précholine des tissus. N'importe quel serait l'antigène et l'anticorps que ce dernier provoque, l'état de paraphylaxie qui se produit à côté consiste toujours en un processus identique: hyperconcentration en précholine. Ainsi donc, la *paraphylaxie n'est pas spécifique*.

Nous avons constaté que dans l'asthme paraphylactique la réaction locale (bronchique) à l'adrénaline ou à l'atropine est la même n'importe quel serait l'antigène qui a provoqué l'état asthmatique: elle prouve un état d'hyperconcentration en précholine. Si ce qu'on appelle anaphylaxie était un état spécifique dû à la formation d'anticorps spécifiques, l'état des tissus serait différent suivant l'antigène qui a provoqué les phénomènes. Il en est de même pour les états de paraphylaxie générale.

E. *L'état d'hyperconcentration en précholine pendant la paraphylaxie est le même que l'état d'hyperconcentration précholinique tissulaire du à d'autres causes.*

L'amphotonique constitutionnel réagit à l'adrénaline et à l'atropine de la même manière que l'amphotonique paraphylactique. Dans l'asthme non paraphylactique les bronches réagissent de la même manière à l'adrénaline et à l'atropine que dans l'asthme paraphylactique. Dans les deux cas il s'agit d'un état d'hyperconcentration en précholine et ce n'est que la pathogénie de ce dernier état qui est différente.

F. *Étude de l'asthme paraphylactique et non paraphylactique.*

Voici notre conception sur le mécanisme de l'accès d'asthme exposé en 1931, l'accès d'asthme se produit sur un terrain prédisposé *localement*. La tuberculose, qui se trouve très souvent dans les antécédents des asthmatiques, évoluant vers la sclérose, laisse dans les bronchioles et leurs nerfs des lésions inflammatoires irritatives qui augmentent leur réactivité et provoquent un état d'hypertonie locale. Selon notre «loi des prédominances» chaque fois qu'un organe est en état d'hypertonie tous les facteurs qui agissent tant dans le sens sympathique que parasympathique, prédominent plus que normalement dans le sens du nerf excitateur, qui pour les bronches est le parasympathique. Cette lésion constitue le *facteur prédisposant anatomique*. A ce dernier s'ajoute un état d'immunité locale (*facteur prédisposant phylactique*) produite par les albumines altérées résultant de la destruction tissulaire qui, devenant des albumines hétérogènes, constituent des antigènes qui provoquent localement un état d'immunité (et non de sensibilité) locale. Les anticorps se produisent en étroite union avec l'acétylcholine et l'état de *phylaxie locale* s'accompagne d'un état de *paraphylaxie locale*, qui n'est qu'une hyperconcentration locale en précholine. Cette hyperconcentration en précholine reconnaît par conséquent deux sources: la lésion anatomique des bronches et des nerfs et la paraphylaxie locale. La source de précholine des tissus bronchiques étant plus riche, tout facteur acétylcholinergique libère plus d'acétylcholine que normalement. L'accès

d'asthme peut être provoqué chez ces sujets, par un facteur nerveux (un réflexe par exemple) ou par la formation locale d'un complexe phylactique (antigène-anticorps-alexine). Les réflexes sont tous amphotropes et prédominent plus que normalement sur le groupe exciteur (parasymphatique) toutes les fois que l'organe se trouve en état d'hypertonie. Il se produit une libération exagérée d'acétylcholine qui déclenche la bronchoconstriction. Chez le même individu la réintroduction dans l'organisme du même antigène qui a provoqué l'état d'immunité locale provoque la formation d'un complexe phylactique (antigène-anticorps-alexine) qui libère de l'acétylcholine, substance qui provoque la bronchoconstriction.

Ainsi donc, ces sujets peuvent faire des accès *d'asthme non paraphylactique* produits par un réflexe ou un état *paraphylactique* produit par la réintroduction du même antigène.

L'état de prédisposition anatomique peut être dû à une lésion broncho-pneumonique ou aux gaz asphyxiants ou à une blessure du poumon. L'état de phylaxie et de paraphylaxie locale peut être provoqué par l'inhalation de différents antigènes: émanation de mouton ou de cheval, poudre d'ipéca, pollen de graminées, etc.

Cet état de phylaxie et de paraphylaxie locale produit par l'antigène peut être accompagné d'un état de phylaxie et de paraphylaxie générale due au passage d'une petite partie de l'antigène dans la circulation. Mais c'est surtout l'état local qui prédomine. D'un autre côté lors de la formation du complexe phylactique local (par la réintroduction du même antigène), l'acétylcholine libérée en grande quantité peut passer aussi dans le sang. C'est de cette manière que s'explique le fait que le choc local s'accompagne d'un choc général (hypotension, leucopénie avec mononucléose et éosinophilie). Mais c'est toujours le choc local qui prédomine.

L'étude de l'asthme paraphylactique et non paraphylactique nous donne une série de preuves et d'arguments en faveur de notre hypothèse. Nous en avons déjà parlé dans les paragraphes antérieurs et nous ne faisons ici que les résumer.

a) La symptomatologie de l'accès d'asthme paraphylactique ressemble aux phénomènes provoqués par l'acétylcholine: bronchoconstriction, phénomènes vasculaires et glandulaires bronchiques, éosinophilie locale, hypotension, leucopénie générale avec mononucléose et éosinophilie.

Expérimentalement nous avons provoqué chez le cobaye et le lapin neuf le syndrome de l'asthme par une injection intra-trachéale d'acétylcholine. La lésion anatomique est identique à celle décrite dans le choc dit anaphylactique. Comme ce dernier les phénomènes d'asthme sont empêchés par l'atropine.

b) N'importe quel serait l'antigène qui a provoqué l'état d'immunité locale, le syndrome asthmatique est identique, car l'état de paraphylaxie consiste toujours en une hyperconcentration en précholine et l'accès est provoqué toujours par l'acétylcholine.

c) symptomatologie de l'accès d'asthme paraphylactique est identique à la symptomatologie de l'accès d'asthme non paraphylactique dû à un facteur nerveux (réflexe, etc).

Dans les deux cas il s'agit de libération d'acétylcholine.

d) Les bronches chez les sujets prédisposés à l'asthme paraphylactique réagissent à l'adrénaline comme dans l'asthme non paraphylactique. Une dose amph S (bronchodilatatrice) est dans ces cas amph P (bronchoconstriction).

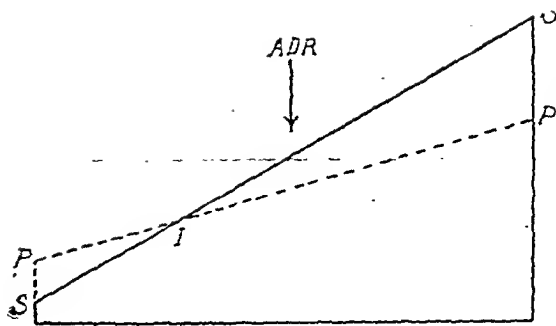
Il en est de même pour la réaction à l'atropine.

Nous avons démontré le phénomène intéressant suivant. Chez un asthmatique il existe un état de paraphylaxie bronchique intense, accompagné souvent d'un état de paraphylaxie générale très faible, qui peut ne pas exister. L'épreuve à l'adrénaline et à l'atropine (à une certaine dose) donne dans ces cas un effet normal ou quasi normal sur le cœur (tachycardie) et les vaisseaux (hypertension) et un effet inversé sur les bronches. C'est ce que nous avons constaté dans l'asthme en employant certaines doses d'adrénaline ou d'atropine.

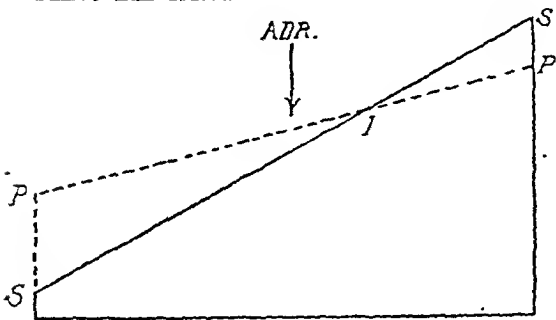
Une injection d'adrénaline nous a donné une tachycardie et une élévation de la pression sanguine (action amph S) et en même temps une exagération de l'accès d'asthme par bronchoconstriction (action amph P). Le phénomène est dû à une hyperconcentration des bronches en précholine et une concentration moindre en cette prés substance du cœur et des vaisseaux (fig. 3).

Chez le même malade il fallait une dose plus forte d'adrénaline pour arriver à une bronchodilatation (action amph S).

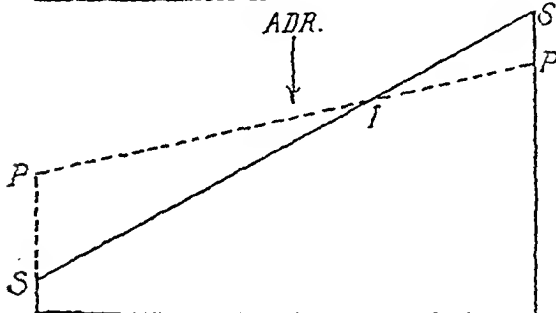
L'atropine nous a donné des résultats concordants. La dose de $\frac{3}{4}$ mg de sulfate d'atropine injecté sous la peau a donné une accélération du rythme (action parasympatho-frénatrice) et une exa-



ACTION DE L'ADRENALINE
SUR LE CŒUR ET LES
VAISSEAUX CHEZ UN
SUIET NORMALET CHEZ
UN ASTHMATIQUE



ACTION DE L'ADRENALINE
SUR LE CŒUR, LES
VAISSEAUX ET LES
BRONCHES APRÈS
L'ESÉRINE



ACTION DE L'ADRENALINE
SUR LES BRONCHES
CHEZ UN ASMATIQUE

Fig. 3. — Nous avons démontré que l'adrénaline est amph P à petite dose et amph S à grande dose. L'adrénaline a une action directe S-mimétique (réponse cellulaire) qui déclenche une riposte cellulaire compensatrice par libération d'AChE. Il est naturel que plus la concentration des tissus en CACH sera élevée, plus la quantité d'AChE libérée cependant la riposte sera grande. Une petite dose d'adrénaline déclenche une quantité d'AChE dont l'action P-mimétique dépasse l'action directe S-mimétique de l'adrénaline. Au fur et à mesure que nous nous rapprochons de la dose iso-mimétique, la prédominance parasympathique est moindre. C'est que l'action S-mimétique de l'adrénaline croît avec la dose plus vite que son action P-mimétique. La même dose d'adrénaline provoquera la libération de plus d'AChE dans une cellule qui contient plus de préchole. La figure 3 montre que lorsque la concentration en préchole est élevée, une dose qui sur un organe normal est amph S, devient amph P.

Nous avons déjà décrit cette action inversée de l'adrénaline dans l'état de parasympathie générale (corollaire de l'état de phylaxie générale). Elle est très nette dans l'état de parasympathie locale bronchique.

Nous avons eu des malades atteints d'asthme chez lesquels la dose thérapeutique classique d'adrénaline provoquait une tachycardie (action amph S) et en même temps exagérait la bronchoconstriction (action amph P). Chez un sujet normal, il existe certaines différences dans l'action de l'adrénaline entre les différents organes. Mais la différence que nous avons trouvée chez les asthmatiques, entre, les bronches d'une part et l'appareil circulatoire de l'autre, est infiniment plus grande. Le fait que chez le même sujet la même dose d'adrénaline produit sur les organes normaux une action amph S et sur les bronches une action amph P, ne laisse plus aucun doute sur l'état d'hyperconcentration locale en préchole qui caractérise l'état de parasympathie locale (corollaire de l'état de phylaxie locale) au niveau des bronches.

gération de l'accès d'asthme par bronchoconstriction (action amph P). Et il faut une plus grande dose d'atropine pour obtenir une bronchodilatation. La limite entre la dose amph P et p-frénatrice d'atropine est située d'autant plus haut que la concentration en précholine des tissus est plus élevée.

G. — Si l'anaphylaxie était spécifique (due à des anticorps sensibilisants spécifiques) l'antianaphylaxie devrait être aussi spécifique.

Elle devrait n'apparaître qu'en injectant l'antigène correspondant. Or, nous pouvons réaliser ce qu'on appelle anti-anaphylaxie par des moyens non spécifiques.

On soutient, depuis Besredka, que ce qu'on appelle anti-anaphylaxie est due à l'épuisement des anticorps dû à l'injection dite anti-anaphylactisante. Lors de l'injection anti-anaphylactisante, l'antigène spécifique s'unit aux anticorps anaphylactisants et l'antigène injecté le lendemain ne trouve plus d'anticorps anaphylactisants spécifiques grâce auxquels est libérée l'anaphylatoxine.

Mais nous pouvons obtenir le phénomène d'antianaphylaxie avec les mélanges d'antigène anticorps *in vitro*. Nous injectons à un cobaye neuf une petite dose de ce mélange (incapable de provoquer un choc mortel) et le lendemain une nouvelle dose du même mélange qui produit chez le témoin (non injecté la veille) un choc mortel. Dans cette expérience il ne peut plus être question d'épuisement des anticorps, qui se trouvent dans notre mélange fait *in vitro*.

D'un autre côté, il est prouvé que nous pouvons obtenir le phénomène d'anti-anaphylaxie avec la peptone, avec la tuberculine, avec un autre antigène que celui qui a été employé pour préparer l'animal.

L'anti-anaphylaxie n'est par conséquent pas spécifique, ce qui serait incompréhensible si nous admettons que l'anaphylaxie est spécifique et que le phénomène d'anti-anaphylaxie est dû à l'épuisement des anticorps.

Seule notre conception peut expliquer cette contradiction qui, à elle seule, fait tomber l'idée de l'anaphylaxie spécifique. Et si l'anaphylaxie n'est pas spécifique, l'hypothèse entière d'une anaphylaxie, provoquée par des anticorps anaphylactisants et constituant un état indépendant et opposé à l'immunité, tombe.

Voici notre explication.

Un sérum étranger, la tuberculine, la peptone libèrent de l'acétylcholine, et épuisent la précholine tissulaire. Lors de la deuxième injection (d'une dose mortelle chez le témoin) la concentration en précholine des tissus est trop faible et la quantité d'acétylcholine libérée trop petite pour provoquer un choc évident.

Il s'agit par conséquent d'un phénomène anti-paraphylactique, car le choc paraphylactique est dû à la libération d'acétylcholine. Lorsque nous employons l'antigène spécifique pour provoquer le phénomène anti-paraphylactique voici ce qui se produit. Il y a dans ces cas en même temps épuisement des anticorps et épuisement de précholine. La première injection (anti-paraphylactisante) d'antigène provoque la formation d'un complexe immunisant ou phylactique (et non pas un complexe anaphylactique) qui immobilise une partie des anticorps et libère de l'acétylcholine. Mais la quantité d'antigène injecté étant trop petite, une partie seulement des anticorps est fixé et la quantité d'acétylcholine injectée n'est pas suffisante pour provoquer un choc grave. Lorsque nous injectons le lendemain la deuxième dose d'antigène, et les anticorps et la précholine se trouvent en quantité insuffisante pour déclencher un choc évident.

Dans ce cas il y a, comme nous l'avons dit plus haut, épuisement tant des anticorps que de précholine. Mais l'épuisement de la précholine suffit car nous pouvons provoquer le phénomène anti-paraphylactique par un facteur acétylcholinergique non spécifique.

Nous n'avons d'ailleurs qu'épuiser la précholine des tissus par le jeûne ou par la production de fièvre pour obtenir le même phénomène anti-paraphylactique.

Une expérience tout aussi concluante est celle que nous pouvons faire avec la suspension de gélose, dans l'expérience de Bordet. Cet auteur a soutenu qu'une injection intra-veineuse de gélose chez l'animal neuf provoque la libération d'anaphylatoxine qui produit un choc anaphylactique classique. Nous soutenons qu'il n'y a là que production d'un choc acétylcholinique, dû à l'action acétylcholinergique de la gélose et qui n'a rien à faire avec l'anaphylaxie.

Eh bien, nous pouvons, par une injection préalable d'une petite quantité de gélose, empêcher le choc acétylcholinique d'une dose de gélose mortelle chez le témoin. La première injection d'une petite dose de gélose a libéré une certaine quantité d'acétylcholine qui a épuisé la précholine tissulaire.

H. Rôle des anticorps pendant l'incubation d'une maladie spécifique.

Nous pouvons supprimer l'incubation de la maladie spécifique en fournissant à l'organisme les anticorps nécessaires en même temps que l'antigène et en provoquant de la sorte un choc paraphylactique acétylcholinique qui déclenche la maladie spécifique.

Nous savons que si nous injectons à un animal neuf un antigène mélangé à du sérum d'un autre animal préparé par le même antigène (et par conséquent en état de phylaxie et de paraphylaxie) nous obtenons le choc dit anaphylactique. C'est ce qu'on a appelé anaphylaxie *in vitro* et qui n'est en réalité qu'un phénomène paraphylactique produit à côté d'un phénomène d'immunité *in vitro*. Le sérum de l'animal ainsi préparé contient les anticorps spécifiques (immunisants) qui avec l'antigène injecté en même temps et l'alexine trouvée dans l'organisme de l'animal neuf injecté avec ce mélange forment un complexe phylactique (immunisant) qui libère de l'acétylcholine, laquelle provoque le choc paraphylactique acétylcholinique. Il s'agit en réalité de la formation d'un complexe phylactique (et non pas d'un complexe anaphylactique) qui libère de l'acétylcholine.

Lorsque l'antigène, injecté en même temps que l'anticorps, a été fixé intégralement par ce dernier il se produit un choc paraphylactique acétylcholinique. Le complexe phylactique qui déclenche le choc représente un phénomène d'immunité complète. Mais si l'antigène n'a pas été fixé intégralement par l'anticorps et qu'il reste une partie libre, non fixée, il se produit un choc paraphylactique acétylcholinique suivi de maladie spécifique. Et c'est le choc qui favorise l'action spécifique de la fraction d'antigène qui reste libre. C'est ce qui s'est passé dans nos expériences faites avec la toxine diphtérique.

Nous avons dit que les complexes phylactiques formés avec des anticorps qui agissent sans alexine, libèrent peu d'acétylcholine à la fois et ne provoquent pas de choc évident. C'est le cas de l'antitoxine diphtérique. Un mélange de toxine-antitoxine diphtérique injectée au cobaye neuf dans la veine ne produit pas de choc.

Mais si nous préparons l'animal à l'ésérine, qui favorise l'intervention de l'acétylcholine, le choc devient évident. Chez une série de cobayes ésérinisés nous injectons dans la veine un mélange neutre de toxine-antitoxine diphtérique. Chez une partie de ces

cobayes il s'est produit un choc paraphylactique acétylcholinique (ancien choc anaphylactique) classique, chez les uns mortels.

Chez une autre partie le choc a été suivi en quelques minutes d'une paralysie du train postérieur. Ce phénomène est spécifique dans l'action de la toxine diphtérique. Mais lorsque nous injectons la toxine seule, la paralysie du train postérieur apparaît après une période d'incubation qui est nécessaire à la production des anticorps. Lorsque avec la toxine nous injectons aussi l'antitoxine, la période d'incubation n'est plus nécessaire et le phénomène spécifique apparaît sans incubation, favorisé par le choc paraphylactique acétylcholinique. Cette expérience démontre d'une manière évidente que:

— c'est le choc paraphylactique acétylcholinique qui déclenche la maladie spécifique,

— l'incubation est nécessaire à la production des anticorps, sans lesquels le complexe phylactique ne peut pas se produire, et non plus le choc qui déclenche la maladie spécifique.

Il y a dans cette expérience un phénomène qu'il faut expliquer. Le mélange de toxine antitoxine injecté était un mélange neutre. Tout l'antigène était fixé par l'anticorps et il ne restait aucune fraction d'antigène libre qui puisse provoquer des phénomènes spécifiques. Il est possible que sous l'influence du choc paraphylactique produit, le complexe toxine-antitoxine ait libéré une partie de la toxine, laquelle a provoqué la paralysie du train postérieur. *Mais cette paralysie s'est produite sans incubation, grâce au choc paraphylactique qui l'a déclenché. Et ce choc ne pouvait pas se produire sans la présence des anticorps.*

I. — Le début d'une pneumonie est un choc paraphylactique acétylcholinique suivi de phénomènes spécifiques (phénomènes d'immunité incomplète) et la défervescence est un choc paraphylactique acétylcholinique pur, non suivi de phénomènes spécifiques (phénomène d'immunité complète). Etude d'autres infections (fig. 4 et 5).

Nous avons eu quatre pneumonies franches et nous pouvons décrire exactement le début et la fin. L'incubation a été très courte, la plus courte de 6 heures. Le début commence par une hypothermie, un état de collapsus, bradycardie, pouls filant (hypotension). Ce sont des phénomènes acétylcholiniques, après lesquels commence le frisson, avec ascension brusque de la température, leucocytose, tachycardie, point de côté, toux sèche. Tous

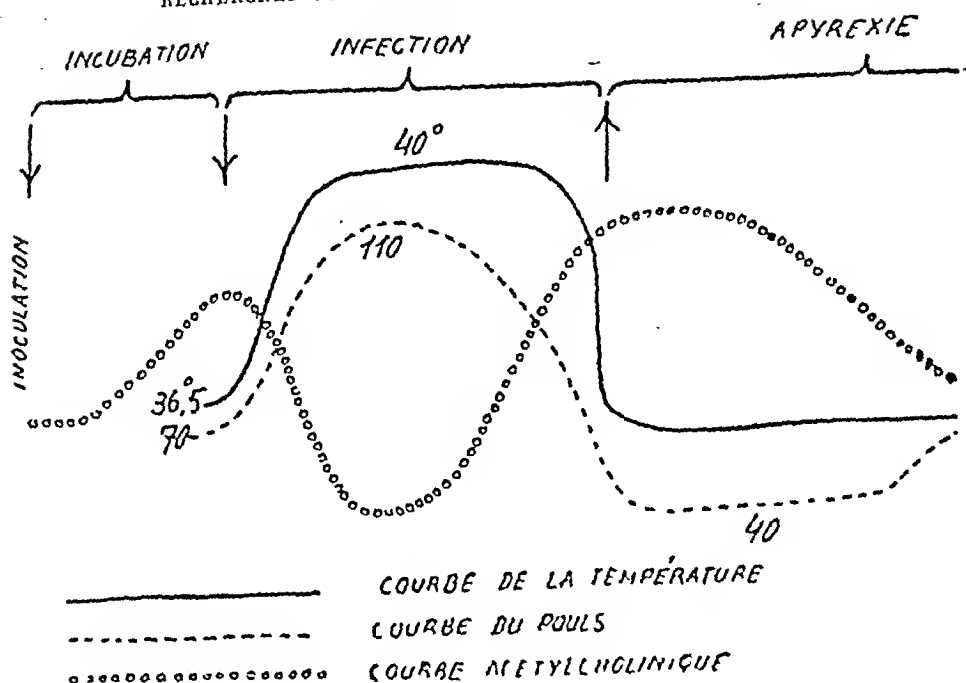


Fig. 4. — Courbe acétylcholinique dans une infection qui guérit. Nous prenons l'exemple d'une infection à incubation de 8 jours, avec début et terminaison assez rapides, avec une période fébrile de 14 jours, terminée par la guérison.

L'antigène provoque pendant l'incubation la formation d'anticorps qui se produisent, comme toujours, en étroite union avec l'acétylcholine: la courbe acétylcholinique monte. La libération de l'acétylcholine est assurée par l'action acétylcholinergique de l'antigène et de l'acide p-aminobenzoïque lequel assure aussi la multiplication des microbes. Lorsque les anticorps-choline sont arrivés dans les tissus à un degré de concentration suffisante, il se produit avec l'antigène qui est en circulation et l'alexine un complexe antigène-anticorps-alexine qui est accompagné d'un choc paraphylactique acétylcholinique. Mais ce complexe n'a pas fixé tout l'antigène (phénomène d'immunité incomplète) et la partie qui reste libre sous l'action favorisante du choc, provoque la maladie spécifique.

Les phénomènes spécifiques consomment l'acétylcholine: d'où tachycardie. L'antigène continue à libérer de l'acétylcholine et à provoquer la formation des anticorps-choline. Vers la fin de l'infection la courbe acétylcholinique monte (bradycardie relative, leucopénie relative avec mononucléaires) en même temps que la concentration en anticorps. Lorsque ces derniers sont arrivés à une concentration suffisante, il se produit un complexe antigène-anticorps-alexine avec choc paraphylactique acétylcholinique. Ce complexe fixe intégralement l'antigène (phénomène d'immunité complète). Les phénomènes spécifiques disparaissent. Au moment de la déservescence et les premiers jours de la convalescence se produisent des phénomènes dus à l'acétylcholine libérée pendant le choc: sueurs profuses, polyurie, hypotension, bradycardie, leucopénie avec mononucléaires et éosinophilie.

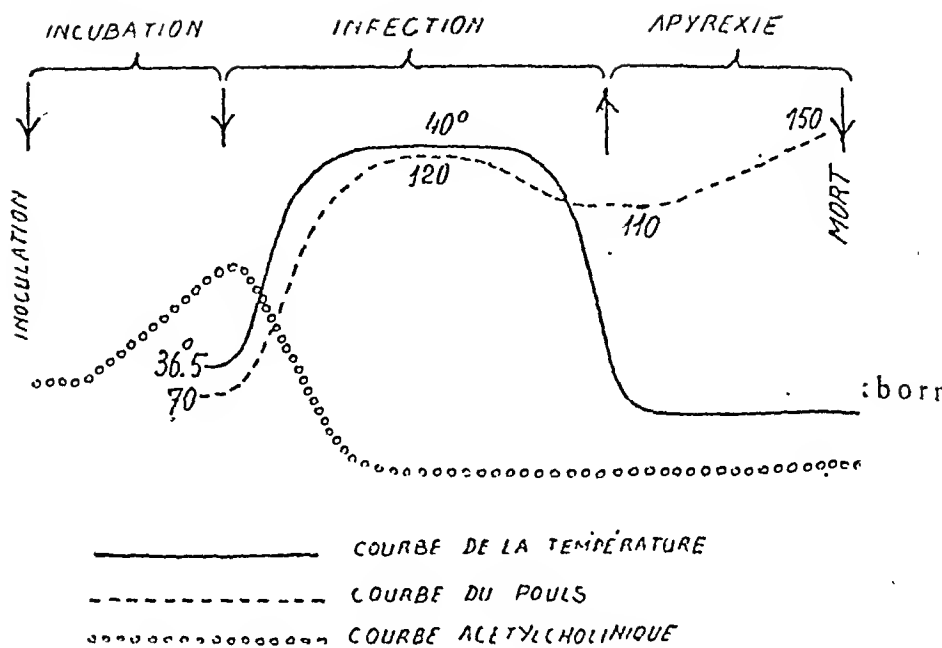


Fig. 5. — Courbe acétylcholinique dans une infection qui se termine par la mort.

Exemple d'une forme hypertoxique de typhus. Comparer avec la figure 89.

La courbe acétylcholinique baisse progressivement jusqu'à la mort, la tachycardie monte progressivement, la leucopénie n'apparaît pas, les éosinophiles sont absents.

sont des phénomènes spécifiques. Le frisson est dû au passage de l'hypothermie acétylcholinique à la fièvre, qui est un phénomène spécifique. Les phénomènes anatomiques locaux sont des phénomènes spécifiques, préparés par la vasodilatation acétylcholinique.

Pendant l'incubation, l'antigène (produits bactériens du pneumocoque) provoque un état de phylaxie et de paraphylaxie. Lorsque les anticorps sont arrivés à une certaine concentration ils forment avec l'antigène qui reste libre un complexe phylactique qui ne fixe qu'une partie de l'antigène, (phénomène d'immunité incomplète) avec forte libération d'acétylcholine, qui provoque un choc paraphylactique acétylcholinique, lequel déclenche la maladie spécifique (produite par l'antigène resté libre).

Pendant sept jours le pouls est tachycardique (consommation d'acétylcholine par les phénomènes spécifiques). Pendant ce temps l'antigène continue son action acétylcholinergique et la production d'anticorps-choline. Vers le 7-ème jour, à un moment où la

concentration en anticorps-choline est arrivée à un degré suffisant, ils fixent intégralement l'antigène resté libre et forment un complexe phylactique (phénomène d'immunité complète) avec choc paraphylactique acétylcholinique pur. L'hypothermie, les sueurs profuses, la leucopénie avec mononucléose et éosinophilie, la bradycardie, l'hypersécrétion urinaire sont des phénomènes acétylcholiniques.

Nous avons étudié la marche de la courbe acétylcholinique par notre épreuve de l'atropine et de l'orthostatisme dans le *typhus exanthématique*, maladie où le début et la fin sont moins brusques que dans une pneumonie et dans la fièvre typhoïde où le début est progressif et la défervescence en lysis.

Dans le typhus exanthématique l'hyperthermie maxima met 36 à 48 heures pour se produire et la défervescence se fait aussi plus lentement en 24—48 heures. Les phénomènes de choc du début et de la fin sont moins nets. Ils sont beaucoup moins nets dans la fièvre typhoïde où le début et la fin se produisent progressivement. Mais dans toutes les maladies infectieuses il s'agit de phénomènes paraphylactiques, consécutifs à la formation de complexes phylactiques, et déclenchant les phénomènes spécifiques.

La période amphibole qui apparaît souvent dans la fièvre typhoïde est très intéressante. En comparant les phénomènes que présente le malade le matin (hypothermie, bradycardie, etc) et le soir (ascension thermique, tachycardie), nous avons l'impression d'une série de chocs paraphylactiques produits quotidiennement suivis de phénomènes spécifiques qui ont leur maximum vers le soir. Les complexes phylactiques, qui donnent naissance à ces chocs représentent des phénomènes d'immunité incomplète, dans lesquels une partie seulement de l'antigène est fixée, le reste de cet antigène produisant les phénomènes spécifiques. A mesure que les anticorps augmentent en concentration les phénomènes d'immunité deviennent de plus en plus complets et lorsque tout l'antigène a été fixé et rendu inoffensif se produit l'apyrexie,

Dans toutes les maladies infectieuses nous rencontrons par conséquent au début et à la fin, certains phénomènes semblables, ceux qui sont produits par l'acétylcholine, libérés pendant les phénomènes d'immunité incomplète, auxquels s'ajoutent des symptômes spécifiques dus à l'action de l'antigène qui n'a pas pu être fixé et qui exerce son action à la faveur du choc paraphylac-

tique. Tout naturellement ces phénomènes sont différents d'une maladie à l'autre.

Le fait se remarque surtout en étudiant les manifestations locales de chaque maladie. Le début d'une scarlatine, ou d'une rougeole est déclenché par un phénomène d'immunité incomplète et un choc paraphylactique acétylcholinique. L'acétylcholine, par son action vasodilatatrice prépare le terrain pour la lésion spécifique. Dans les trois maladies nous rencontrons cette vasodilatation générale, mais l'exanthème qui apparaît ensuite sur ce fond de vasodilatation est différent car il s'ajoute l'action spécifique de l'antigène qui naturellement est différente suivant l'agent microbien. La même vasodilatation acétylcholinique se produit aussi au début de la maladie du sérum, mais l'exanthème sérique est tout spécial, différent de l'exanthème rougeoleux ou scarlatineux, car il s'ajoute l'action spécifique de l'antigène. La vasodilatation acétylcholinique initiale explique les phénomènes congestifs locaux qui se produisent si rapidement dans une pneumonie, mais la lésion prend ensuite un caractère spécifique par l'action spécifique de l'antigène pneumococcique. Dans les congestions pulmonaires de la maladie du sérum, il ne manque pas non plus la vasodilatation acétylcholinique initiale, mais il s'ajoute l'action spécifique de l'antigène qui donne à la lésion des caractères tout différents de la lésion pneumonique.

I. — *Accidents produits chez l'homme par un sérum étranger.*

Les accidents produits par un sérum étranger chez un sujet qui n'avait jamais reçu d'injection du même antigène est un choc acétylcholinique pur (hypothermie, bradycardie, hypotension) qui n'a rien à faire avec l'immunité ou avec la paraphylaxie. La maladie du sérum qui apparaît 8 à 12 jours après une seule injection de sérum étranger est une maladie spécifique déclenchée par un choc paraphylactique acétylcholinique (phénomène d'immunité incomplète). Nous trouverons tout naturellement au début des phénomènes acétylcholiniques qui ressemblent à ceux produits par tout choc paraphylactique suivis de phénomènes spécifiques provoqués par l'action spécifique du sérum et qu'aucun autre antigène n'est capable de produire. La bradycardie, l'hypotension initiale, la tendance au collapsus, la leucopénie avec mononucléose et éosino-

philie sont des phénomènes acétylcholiniques, alors que les phénomènes cutanés, articulaires et névritiques, l'ascension thermique secondaire sont des phénomènes appartenant à la maladie spécifique. Grâce au caractère spécifique de ces phénomènes l'exanthème sérique se différencie nettement des exanthèmes des maladies éruptives.

J. Le choc dit anaphylactique n'est pas un choc histaminique. L'histamine peut intervenir à titre secondaire, surtout dans certains tissus.

Il y a des différences capitales entre le choc paraphylactique acétylcholinique et le choc histaminique.

Le premier est empêché par l'atropine, par une injection de glucose, par le jeûne et par une première injection d'une petite dose du même antigène (Martrou), le second n'est pas empêché ni par l'atropine, ni par le glucose ni par le jeûne. Et une petite dose d'histamine ne prémunit pas contre une dose mortelle de la même substance.

Nous avons fait à ce sujet une expérience qui ne laisse plus aucun doute que le choc dit anaphylactique n'est pas histaminique.

Nous prenons un certain nombre de cobayes inoculés depuis 15 jours avec du sérum de cheval et qui sont par conséquent en état de paraphylaxie et nous les partageons en quatre lots.

Le premier lot reçoit dans la veine une très petite dose du même antigène (qui ne produit pas un choc mortel) et le lendemain toujours dans la veine une dose qui chez les témoins (cobayes en état de paraphylaxie mais n'ayant pas été injectés la veille) est mortelle. Aucun ne meurt.

Le second lot est injecté avec une petite dose d'antigène et le lendemain avec une dose d'histamine qui est mortelle chez le témoin. Tous meurent.

Le troisième lot est injecté avec une petite dose non mortelle d'histamine et le lendemain avec une dose de sérum, mortelle chez les témoins. Tous meurent.

Le quatrième lot est injecté avec une petite dose d'histamine et le lendemain avec une dose mortelle d'histamine. Tous meurent.

Ainsi donc, seulement le même antigène prémunit contre le choc. L'histamine ne prémunit pas contre le choc paraphylactique,

ni l'antigène contre le choc histaminique, ni l'histamine contre le choc histaminique.

Le phénomène produit dans le premier lot est appelé anti-anaphylaxie et interprété par une consommation des anticorps lors de la première injection dite anti-anaphylactique. Mais elle se produit aussi lorsque chez le cobaye neuf, nous injectons le premier jour un mélange d'antigène et d'anticorps et le lendemain le même mélange (Bordet). Il ne peut pas dans ce cas y avoir de consommation d'anticorps, car ces derniers sont injectés par nous.

Le phénomène dit anti-anaphylactique s'explique en grande partie par une consommation de précholine lors de la première injection. C'est ce que nous avons appelé *phénomène de décholinisation tissulaire*. Nous l'avons d'ailleurs produit avec n'importe quel facteur acétylcholinique. Une dose d'agar-agar incapable de provoquer un choc mortel prémunit contre une dose mortelle injectée le lendemain. L'effet produit dans le premier lot de cobayes s'explique par le phénomène de décholinisation tissulaire produite par la première injection. L'antigène injecté le lendemain trouve dans les tissus une source de précholine appauvrie et la quantité d'acétylcholine libérée n'est pas suffisante pour provoquer le choc mortel.

Dans le troisième lot l'histamine injectée la veille ne prémunit pas contre le choc, car cette substance ne décholinise pas les tissus. Dans le deuxième lot l'histamine produit la mort car elle n'a pas besoin d'acétylcholine pour agir.

Les auteurs qui soutiennent la nature histaminique du choc ont apporté comme argument le fait que le choc peut être atténué par des substances appelées histaminolytiques, comme le 933 F. Mais il ne faut pas oublier que ces substances ne sont pas anti-histaminiques, mais agissent sur la cellule dont elles modifient le protoplasme et l'empêche de réagir non seulement à l'histamine, mais aussi à la sympathine et l'acétylcholine. C'est ce que nous avons démontré pour les substances 883 F et 933 F.

Nous avons démontré que l'histamine joue un certain rôle dans le choc paraphylactique acétylcholinique, mais ce rôle est secondaire. L'acétylcholine est excitatrice pour la grande majorité des organes de l'économie (tube digestif, muscles bronchiques, canaux urinaires et biliaires, toutes les glandes) et augmente aussi le tonus de l'énorme masse de la musculature volontaire. Tous ces

organes augmentent leur fonctionnement pendant le choc paraphylactique acétylcholinique. Or, toute augmentation du travail des organes amène une hyperproduction de métabolites, donc l'histamine. Il y a par conséquent hyperproduction d'histamine. D'un autre côté l'histamine est un excitant de la terminaison sensitive et provoque par voie réflexe une hyperactivité des organes, avec hyperproduction d'acétylcholine. Enfin l'histamine provoque la formation d'axon-réflexes à travers les collatérales sensibles qui libèrent aussi de l'histamine. Mais le primum movens est l'hyperproduction d'acétylcholine.

Dans les tissus non innervés par le Système nerveux végétatif comme les tissus propres de la peau et des muqueuses (cuti-réaction, urticaire, ophtalmoréaction) l'histamine joue un rôle important. Nous n'avons pu qu'atténuer ces phénomènes par l'atropine. Nous croyons que là encore le premier phénomène qui se produit est une acétylcholinogénèse qui se passe dans les vaisseaux, avec histaminogénèse secondaire.

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The Type of Respiration in Severe Hypoglycemia.

By

KNUD LUNDBÆK.

(Submitted for publication April 28, 1944.)

Following the discovery of insulin, investigators and clinicians very soon became acquainted with the picture of the intoxication, the hypoglycemic syndrome. It differs somewhat in the different animal species. In man the chief symptoms known are perspiration, trembling, hunger, palpitation, headache, diplopia, somnolence, clouded sensorium to deep coma, sometimes with convulsions. All these symptoms are easily observable by the affected subject himself or by his entourage. There is, however, another symptom to which little attention has been paid: during severe hypoglycemia the respiration exhibits characteristic changes.

That abnormalities of respiration occur following administration of insulin to animals was already observed in the first investigations on the effect of insulin (Banting, Best, Collip, Macleod & Noble, 1922). These authors noticed that after administration of insulin to rabbits »rapid shallow breathing of a periodic character» was often seen. In dogs tachypnea is at first observed, during the later action of the insulin the respiration was described as follows: »Inspiration is usually short and jerky, and inspiratory tetanus not infrequent» (Macleod, 1926). In man such symptoms do not as a rule seem to have been observed. The first reports on the

symptoms of insulin poisoning in man (Fletcher & Campbell, 1922; Bornstein & Holm, 1924) do not mention respiratory changes. In Macleod's monograph of 1926 on the effect of insulin, changes in the respiration of rabbits and dogs are mentioned, but no abnormal respiration is reported to have occurred upon administration of insulin to human subjects. Wilder (1940) writes about the respiration: »in subcoma the respirations are frequently noisy and stertorous, in deeper coma they often are so shallow that the patient scarcely seems to breathe» — but he gives no description of the type of respiration. Joslin et al (1940) expressly state as a differentiating symptom between diabetic coma and insulin reaction: »Coma: air-hunger. — Insulin reaction: normal respiration.» In spontaneous hypoglycemia, caused for instance by an insulinoma in which the patient has often been troubled by frequent, severe, and protracted attacks before the case has been diagnosed and treatment instituted, the peculiar type of respiration might have been expected to have been striking. This, however, has not been the case. In the first descriptions of spontaneous hypoglycemia (Harris, 1924); in the first very careful description of an operated case of insulinoma (Wilder, Allan, Power & Robertson, 1927); in Oppenheimer's accurate description of nervous and psychic symptoms in hypoglycemia (1927); and in large general surveys such as Wauchopé's (1933) the typical respiration is not mentioned. The latter author says: »respiratory symptoms are not important, dyspnea sometimes occurs and occasionally bradypnea . . .». Only one author seems to have noticed the abnormal form of respiration. Wadi (1928) in a brief report of a case of Morbus Addisonii with hypoglycemic symptoms describes the changes in respiration as follows: »Die Atmung ist tief und schwer, von plötzlichen Pausen unterbrochen, und mit einem Seufzen einleitender Wiederaufnahme der Atembewegungen.»

Author's observations.

In insulin shock treatment the respiratory symptoms in hypoglycemia are so conspicuous that they may entirely dominate the toxic picture. In connection with a series of metabolic investigations (Lundbæk, 1944), the respiration was in some cases followed into the stages not suitable for taking air samples, and it was

thus possible to register the changes in the respiration at the transition to deep coma.

In the sequel a detailed account will be given of such a typical respiration curve from a single person as well as examples of respiration curves from a number of other persons in increasing degrees of insulin poisoning (Figs. 1—10). The figures show at top the ventilation (per 10 l), then the registration of minutes. Of the two respiration curves the upper one was taken with a thorax pneumograph (inspiration, line running downward; expiration, line running upward). The lower one registers the changes in the ventilation chamber of the respiration mouthpiece (inspiration, teeth turning downward, expiration, teeth turning upward). — At bottom, registration of the movements of the bed.

Respiration curves.

1) F. K. — 2 $\frac{1}{2}$ hours after injection of 120 units.

(For the sake of clarity the curve is divided into random periods.)

I. The depth of respiration varies irregularly. In the middle of the period a quite small post-expiratory plateau with a rudimentary inspiration, possibly abdominal (a). Towards the close a jerky expiration (b).

II. Depth of respiration varying, with a hint of Cheyne-Stokes periodicity. The terminating respirations are abdominal — insignificant deflections of the thorax pneumograph (c).

III. In the middle of the period a jerky expiration (d).

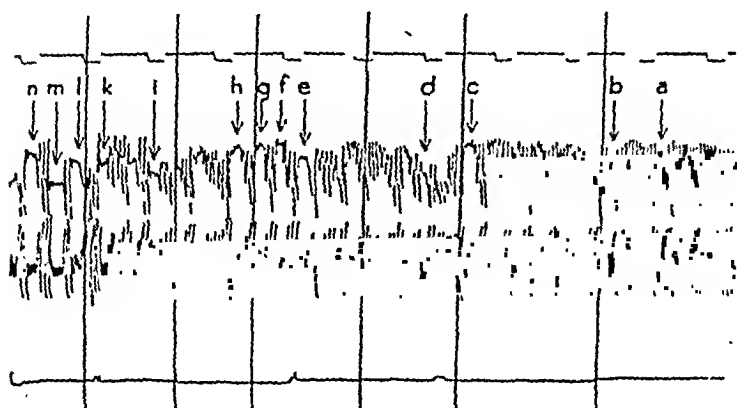
IV. In the middle of the period a long post-expiratory apneic period of 7 seconds (e) — a little later a small irregular post-expiratory plateau in the thorax curve, rudimentary respiration in the pressure curve (f). Similar plateau ultimately with more pronounced (abdominal) inspiration in the pressure curve (g).

V. At first irregular post-expiratory plateau in the thorax curve with two whole abdominal respirations in the pressure curve (h).

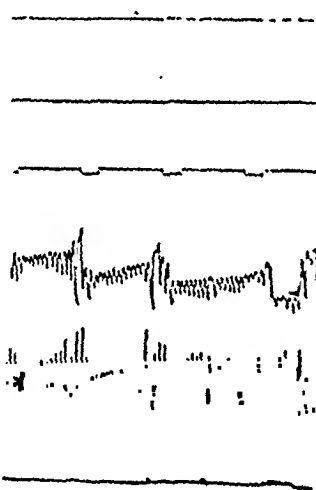
VI. 2 post-expiratory pauses with small rudimentary respiration phases (i.k.).

VII. At first a long jerky expiration of 14 seconds (l), then a couple of deep respirations followed by a post-expiratory pause of 13 seconds (m), again some deep respirations, and another post-expiratory pause of 11 seconds (n).

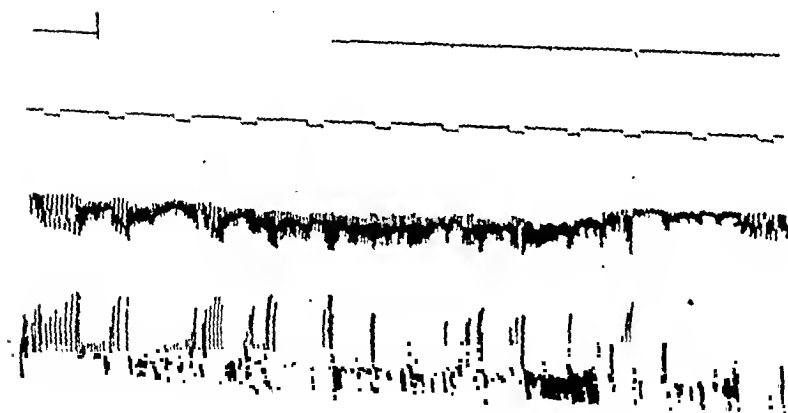
Fig. 1—10: Type of Respiration in varying degrees of hypoglycemia. (For description, see text).



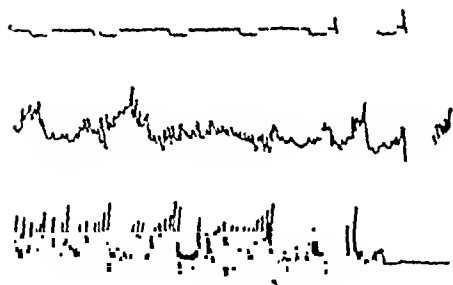
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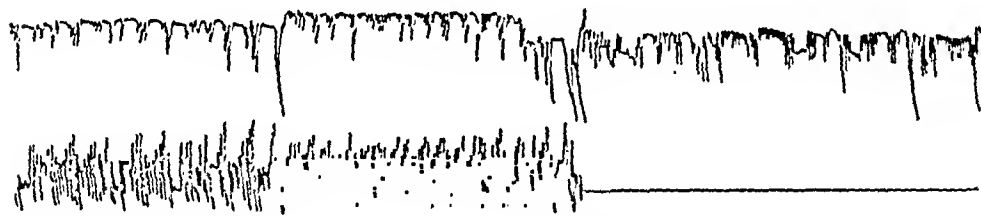
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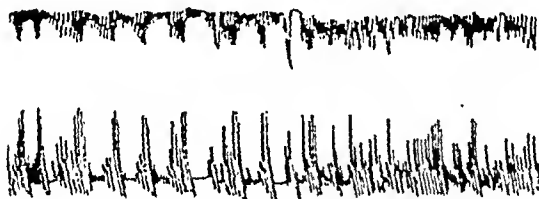
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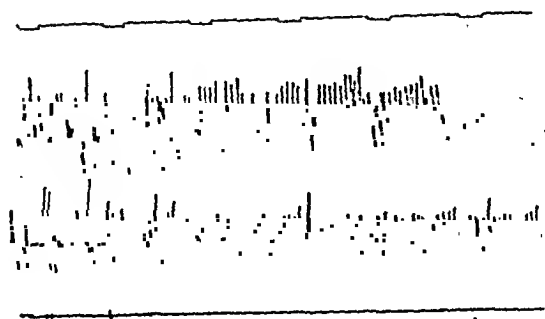
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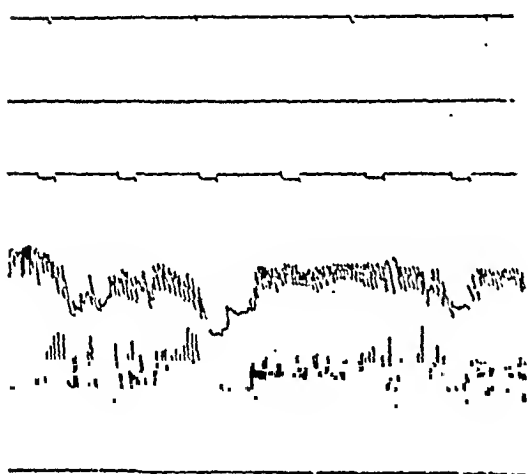
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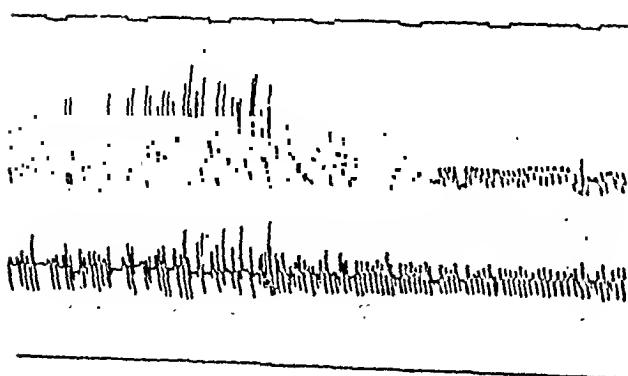
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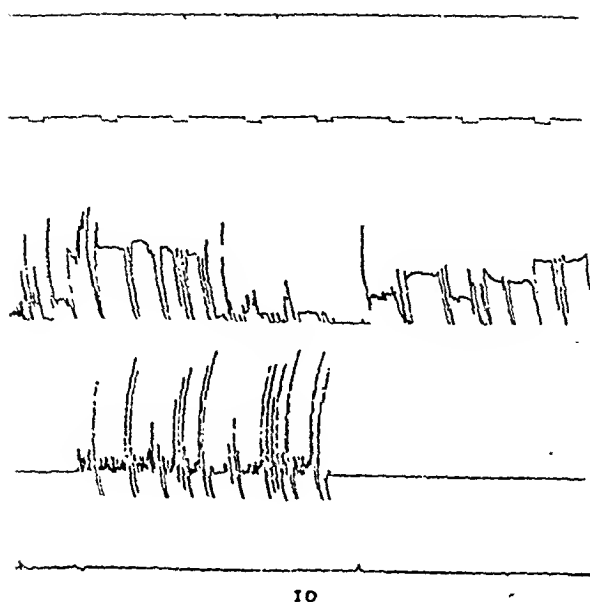
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8



9



Altogether, then, the respiration shows: varying depth, varying thoracic and abdominal respiration, jerky expirations of up to 14 seconds, post-expiratory apnea periods of up to 13 seconds, with rudimentary, sometimes abdominal inspirations.

2) E. G. — 2 $\frac{1}{2}$ hours after injection of 40 units.

Slightly varying respiration of constantly changing type. *Mild case.*

3) H. J. — 2 $\frac{3}{4}$ hours after injection of 264 units.

Constantly changing depth of respiration. Slight changes.

4) M. A. — 2 $\frac{1}{2}$ hours after injection of 24 units.

Varying depth and type of respiration and small post-inspiratory pauses. Thorax curve poor.

5) F. K. — 2 $\frac{1}{2}$ hours after injection of 200 units.

Varying respiration with post-expiratory and post-inspiratory pauses. At first only thorax pneumograph: without mouthpiece, too, quite the same changes are seen.

6) H. J. — 3 hours after injection of 264 units.

Fluctuating depth of respiration and post-expiratory pauses during which the thorax moves with closed glottis. *More pronounced changes.*

7) A. H. — 3 ½ hours after injection of 84 units.

Irregularly varying depth of respiration. Post-inspiratory and post-expiratory pauses, during which the thorax moves vigorously with closed glottis.

8) H. S. — 3 ½ hours after injection of 104 units.

At first fairly regular respiration followed by a post-inspiratory pause. After this, irregular respiration passing gradually into a regular type. In the middle of the period again a very long post-inspiratory apneic period, of ½ minute in all, in the middle interrupted by a brief rapid respiration. After the pause half a score of very vigorous respirations followed by fresh brief post-expiratory and post-inspiratory pauses.

9) A. H. — 3 ¾ hours after injection of 80 units.

At first constantly changing type of the single respirations. Gradually longer pauses with quite small rudimentary deflections in both curves. In the middle of the period a series of jerky expirations. Towards the close, steadily increasing post-expiratory and post-inspiratory pauses during which the thorax moves with closed glottis.

10) H. J. — 3 ½ hours after injection of 168 units.

Constant alternation of extreme respiration movements and pauses of up to 25 seconds during which small rudimentary movements are seen on the pressure curve. *Very pronounced case.*

From the examples given above it appears that during severe hypoglycemia verging on coma characteristic abnormalities of respiration occur, manifesting themselves in 1) varying types of the individual respirations, 2) varying depth of respiration, 3) long jerky expirations and 4) post-inspiratory and postexpiratory apneic pauses. During the apneic pauses rudimentary abdominal respirations are seen in some cases, in other cases the thorax moves vigorously while the glottis is closed.

In pronounced cases the type of respiration described is very striking and easily recognisable. The patient who is as a rule damp and flushed, moves restlessly in bed with stertorous breathing. Deep inspirations alternate abruptly with long pauses during which the thorax is observed to work violently and which quite suddenly terminate in a series of deep respirations. The long jerky exhalation

tions are often accompanied by a vigorous intonation. To this peculiar picture is often added compulsive weeping or laughter, grimacing, pouting lips, gnashing of the teeth, attempts to whistle and the like.

The type of respiration here described is seen during heavy insulin intoxication, often just before the patient passes into deep coma. In this period there are marked psychic disturbances. The patients seem unconscious, but can generally be roused to fairly clear consciousness when spoken to. They are, however, extremely confused and often give inadequate answers, just as their speech itself is marked by aphasia. In some cases the type of respiration described is seen while the patient still seems fairly unaffected in a psychic respect. In such cases it is very curious to observe changes in respiration such as those described, with long apneic pauses, occur in the middle of relatively intelligible talk. The patients do not themselves seem to notice their peculiar respiration, and do not understand if you try to discuss it with them.

When the patient passes into deep coma the respiration often becomes more even, shallow, and rapid. During deep coma too there may, however, again occur irregular respiration. This is especially seen if you try to introduce the mouthpiece, put a clip on the nose, or introduce the stomach tube or the like. The respiration then often reverts to the above described type. After administration of glucose a new phase will in many cases set in before the patient is entirely awake, in which the respiration shows the characteristics described.

The Pathogenesis of the Hypoglycemic Type of Respiration.

The type of respiration here described is part of the severe effect on the central nervous system caused by hypoglycemia. Since the central nervous system is known to oxydize carbohydrate only (Himwich & Nahum, 1932), a hypoglycemic state must be expected to have an elective effect on this tissue which, apart from its own small glycogen store (Kerr & Ghantus, 1936), must resort to nourishment from the blood stream. Investigations by Himwich, Bowman, Wortis & Fazekas (1939) have shown that hypoglycemia involves a greatly decreased absorption of oxygen by the brain tissue, so that in reality there is a hypo-oxidation due to a lack of suitable matter for combustion.

Numerous earlier investigations have shown that there exists a central nervous regulation of the respiration issuing from an automatic »respiratory centre» (Cordier & Heymans, 1935. — Detailed historical survey).

The modern conception of the nervous regulation of the respiration, however, takes its rise from Lumsden's researches (1923). He showed in animal experiments that cutting of the brainstem through the pons gave rise to a peculiar type of respiration which he called »apneustic respiration»; after a deep inspiration there occurs an apnea lasting 2—3 minutes in the maximal position of inspiration, which is replaced by a rapid expiration and a fresh maximal inspiration with postinspiratory apnea, etc. By cutting further down at the level of the striæ acusticæ he observed another form of respiration, the so-called »gasping respiration». In this type respiration consists in a series of gasps with long post-expiratory pauses.

In 1939 Pitts, Magoun & Ranson performed experiments by using Horsley-Clarke's stereotaxic instrument. With this technique they were able to localize two respiratory centres in the medulla oblongata, an inspiratory centre in the formatio reticularis on a level with the cephalic four-fifths of the nucleus olivarius inferior and an expiratory centre just dorsally to this. From the inspiratory centre it was possible to release typical apneustic respirations of arbitrary duration. The authors think it quite possible that there may be a higher-lying pneumotaxic centre governing the two above-mentioned centres.

Besides by stimulation of medullary centres it has often previously been shown that stimulation of other parts of the cerebrum can affect the respiration. With a modern technique Smith (1938) and Bailey & Sweet (1940) showed that stimulation of the premotor zone led to changes in the respiration frequency. Ranson & Magoun (1933) and Ranson, Kabat & Magoun (1935) showed that stimulation of the hypothalamus caused increased depth and frequency of respiration.

Even general influences may give rise to abnormalities of respiration that recall Lumsden's types: gradual ligation of the blood vessels to the cerebrum (Lumsden, 1923); subacute hydrocyanic acid poisoning (Taylor, 1930); and CO₂ poisoning (Barcroft, 1934).

In human pathology abnormal respiration often occurs. In various cases of poisoning, abnormalities of respiration have been described in the form of Cheyne-Stokes respiration, irregular respiration with apneic pauses, violent expirations etc. This applies e.g. to certain phases of barbituric acid, chloral, morphin and carbon monoxide poisoning (Lewin, 1929). Tumors in the pons, medulla oblongata, and the fourth ventricle are said to have caused disturbances in the frequency and rhythm of respiration (Brain, 1933). In chronic encephalitis abnormalities of respiration occur now and again which are highly reminiscent of those found in hypoglycemia (Turner & Critchley, 1925).

As will appear from this, abnormal forms of respiration resembling the above-described type of respiration in hypoglycemia can be produced in animal experiments and are met with in the clinic in local injuries to the central nervous system or in general disturbances of its function. As far as part of the general disorders are concerned we are evidently confronted with the sequelae of a hypooxidation. (Ligation experiments, hydrocyanic acid poisoning, carbon monoxide poisoning etc.).

Since, as already mentioned, such a reduction in the oxidation of the brain also occurs in hypoglycemia, it is only natural that the resulting abnormalities of respiration should resemble those described in other general influences. In spite of the fundamental resemblance — irregular respiration with apneic pauses and varying depth of respiration — it will be seen that none of the above-described experimentally produced respiration types absolutely conform to the hypoglycemic type of respiration. A pure apneustic form of respiration is not observed in hypoglycemia, and of «gasping» respiration there is merely a suggestion in severe cases.

This lack of conformity may possibly be due to the special conditions in the hypoglycemic hypo-oxidation. The small glycogen store of the brain which is very stable in regard to other normally occurring actions such as carbohydrate withdrawal, is known to be used up during the action of insulin (Kerr & Ghantus, 1936). At the same time as the supply of glucose through the bloodstream is reduced to a minimum, an «abnormal» combustion of this store of glycogen takes place. It is possible that this factor is of importance for the special abnormalities in hypoglycemia.

Diagnostic Significance.

The type of respiration here described may be of importance, for the diagnosis of hypoglycemic states. In making the diagnosis, however, the previously mentioned abnormal forms of respiration in other conditions must be taken into account. This applies especially to certain forms of poisoning, brain tumor, and chronic encephalitis.

The type of respiration in hypoglycemia may especially be assumed to become significant in the differential diagnosis between diabetic coma and insulin reaction. This diagnosis, though generally easy, may at first sight cause difficulties in certain cases. The occurrence of a form of respiration such as the above-described will in doubtful cases strongly favour a hypoglycemic state. The negative finding does not exclude that hypoglycemia may be present. Partly the above-described type of respiration is not pronounced in all cases, partly, as previously stated, it only occurs in a certain phase of the hypoglycemia.

In the diagnosis of diabetic coma stress is laid on the acidotic respiration, Kussmaul's respiration. The type of respiration described above is in reality just as «characteristic» of hypoglycemia, as Kussmaul's respiration is of diabetic coma — in none of these cases the abnormalities are specific.

Summary.

A description is given of a characteristic type of respiration which occurs during severe hypoglycemia and which it has been possible to register in connection with metabolic experiments. This type of breathing is characterised by the occurrence of varying depth of respiration, jerky expirations and post-inspiratory and post-expiratory pauses. The pathogenesis of this form of respiration is discussed. It is compared with other forms of abnormal respiration in animal experiments and in the clinic. The conclusion is drawn that it is due to a general hypo-oxidation in the cerebrum possibly of a special kind owing to the special conditions in hypoglycemia. The diagnostic significance of this type of respiration is discussed.

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Recherches sur le fer du sérum chez les vieillards, spécialement par rapport aux ulcères chroniques des jambes.

Par

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(Ce travail est parvenu à la rédaction le 31 Mars 1944).

I.

Est-ce-que la sidéropénie est un phénomène ordinaire dans la vieillesse?

Notre intérêt pour la circulation du fer dans l'organisme a pendant ces dernières années augmenté de plus en plus. Des recherches très intéressantes et donnant des aspects nouveaux ont été faites, entre autres, à ce sujet par les docteurs suédois Vahlquist et Waldenström. Ce dernier a montré le rapport entre les changements dans l'épithélium et les variations dans la circulation du fer.

Pendant ces dernières années mon attention a été portée sur certaines sortes d'ulcères chroniques aux jambes chez les vieilles personnes. J'ai remarqué dans ces recherches qu'il est nécessaire de se faire une idée sur le fer du sérum chez les vieillards, car on ne pouvait pas à priori croire que la teneur du fer chez les vieillards bien portants était la même que chez les personnes bien portantes qui n'ont pas encore atteint la vieillesse. J'ai constaté déjà au commencement de mes examens des malades atteints d'ulcères aux jambes que certains cas avaient des chiffres remarquablement bas même sans anémie et cela a fait que j'ai voulu chercher

un matériel de contrôle chez les vieillards. Ce matériel a été choisi pendant ces deux dernières années parmi la clientèle de l'hôpital Vasa à Gothenbourg. Il ne semble peut-être pas très réussi de chercher un tel matériel de contrôle dans un hôpital au lieu de la chercher par exemple dans un hospice. Cependant si l'on pense que le matériel de contrôle doit être l'objet d'un bon nombre de recherches pour exclusion des maladies latentes possibles parmi ces vieillards on comprend facilement que le matériel de l'hôpital est le seul convenable. Nous avons décidé, mes internes et moi, de faire nos recherches sur des personnes de plus de 70 ans. Le matériel devait remplir les conditions suivantes: les malades ne devaient avoir aucune maladie contagieuse, ni n'en avoir eu pendant les deux derniers mois. Ils ne devaient pas non plus avoir des symptômes de maladie de foie, de maladie du sang ou de tumeur, en cours au moment de l'examen ou nouvellement guérie. Ils devaient avoir une composition du sang normale, une normale réaction de la sédimentation et une réaction de Wasserman négative, et ils ne devaient pas avoir eu une diète pauvre en fer. Il n'était pas facile de trouver parmi le matériel de l'hôpital des cas remplissant ces exigences. Les cas choisis ont été minutieusement examinés et on a fait spécialement attention aux conditions précédemment nommées. De décembre 1941 à novembre 1943 100 cas (50 hommes, 50 femmes) ont été acceptés pour les recherches en question. Dans les anamnèses nous avons surtout pensé aux symptômes cliniques de la sidéropénie et les cas qui ont donné lieu au moindre soupçon à cet égard ont été exclus.

En ce qui concerne ce «matériel normal» de vieillards je n'ai pas trouvé qu'on a constaté dans quelles limites les valeurs d'hémoglobine et de globules rouges peuvent varier, mais ce sujet est l'objet de recherches spéciales, dont nous ne nous occuperons pas ici. D'après ce que je sais il n'y a pas de données sur la valeur normale chez les vieillards.

Les cas qui ont été pris dans le matériel sont ou ont été admis à l'hôpital exclusivement pour des maladies de vieillesse: une forme quelconque d'artériosclérose (a. cérébrale, a. du cœur sans insuffisance cardiaque, suites après des lésions cérébrales), vieilles fractures du col du fémur, cas bénins de diabète, hypertrophie de la prostate, arthrite déformante de la hanche et de la colonne vertébrale.

L'âge des personnes examinées a varié de 70 à 94 ans et est réparti comme suit:

70—75 ans	29 cas	ont été examinés		
76—80 »	27 cas	»	»	»
81—85 »	33 cas	»	»	»
86—90 »	6 cas	»	»	»
après 90 »	5 cas	»	»	»

L'examen du sang a été fait sur les vieillards à jeun et l'hémoglobine a été déterminée avec un appareil de Sahli standardisé (le standard de Haden 100 % = 15.6 g d'hémoglobine). Les examens du fer du sérum ont été faits au laboratoire de l'hôpital de Sahlgren, dont le chef, le professeur Jörgen Lehmann a montré un grand intérêt et a été pour moi d'une grande aide. Dans des cas spéciaux, surtout ceux avec un γ % très bas de fer du sérum, on a fait des examens pour contrôle à des intervalles plus ou moins longs. La méthode employée par le professeur Lehmann est celle de Bröchner-Mortensen (Dans certains cas des examens ont été parallèlement faits par la méthode Heilmeyer).

La composition du sang chez les 100 cas choisis a variée ainsi: chez les femmes l'hémoglobine est restée dans les limites de 75 à 94 % et chez les hommes entre 80 et 100 %. Les globules rouges du sang chez les femmes ont varié entre 4.00 à 5.00 millions et chez les hommes entre 4.10 à 5.10 millions. La réaction de la sédimentation est restée dans tous les cas dans les limites normales. La réaction de Wassermann a été négative dans tous les cas.

La distribution des valeurs du fer du sérum est montrée par deux courbes, ou la valeur de l'hémoglobine dans chaque cas examiné est marquée.

Comme on voit la valeur du fer du sérum est beaucoup plus basse chez les femmes que chez les hommes. La comparaison des valeurs du fer du sérum chez les vieillards dans mon matériel, avec la valeur, donnée comme normale chez les adultes (d'après Vahlquist 1941) se voit dans la table II. Comme valeur normale pour les vieillards, de plus de 70 ans, on a trouvé pour les femmes une valeur du fer du sérum du $83.6 \pm 4.57 \gamma$ et pour les hommes $108.5 \pm 4.89 \gamma$ %.

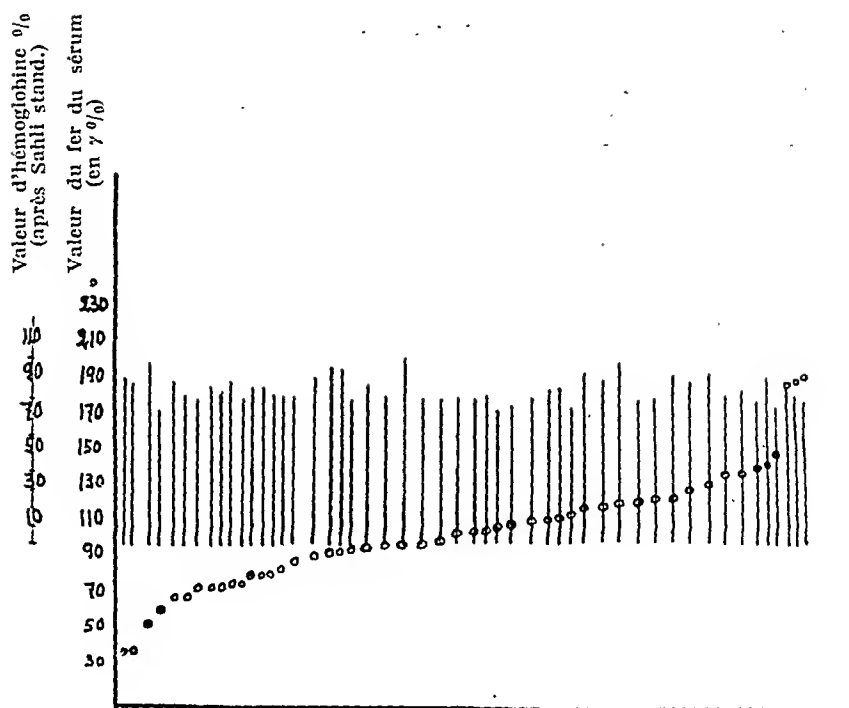


Fig. 1 a. Les valeurs de l'hémoglobine et du fer du sérum chez les vieillards (hommes).

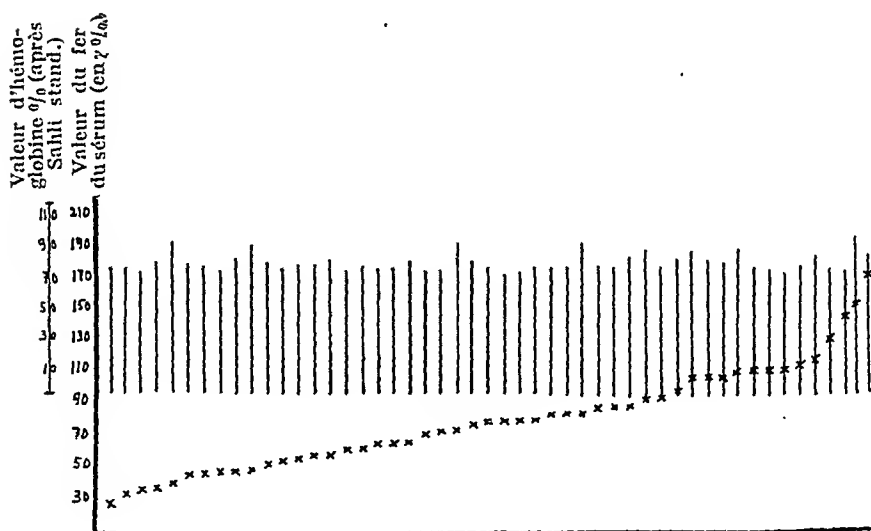


Fig. 1 b. Les valeurs de l'hémoglobine et du fer du sérum chez les vieillards (femmes).

Table II.

Les valeurs du fer du sérum (valeur normale) chez les adultes (d'après Wahlquist 1941) comparées avec les valeurs chez les vieillards.

Valeur normale, adulte	Valeur moyenne	Valeur normale, vieillard	Valeur moyenne
Femme 26—182 γ %	103.5 ± 2.5 γ %	30—171 γ %	96.6 ± 4.57 γ %
Homme 55—191 γ %	122.7 ± 2.2 γ %	40—196 γ %	108.5 ± 4.89 γ %

Nous trouvons donc chez le vieillard et des valeurs moyennes plus basses chez les deux sexes, et une différence évidente de sexe (comme chez les jeunes) avec des valeurs beaucoup plus basses chez la femme, différence qui est statistiquement prouvée.

Dans un certain nombre de cas, il a été possible d'examiner la présence d'achylie réfractaire à l'histamine. J'ai dans la table III inscrit ces cas, et je les ai partagés en ce qui concerne les valeurs du sérum du fer en un groupe au-dessous de 60 γ % et en un groupe au-dessus de cette limite. Comme l'on voit il y a 13 de ces 52 cas examinés qui ont une valeur de fer du sérum au dessous de 60 γ % et parmi ces cas il y a 11 femmes. Aucune différence pour la sidéropénie chez les cas avec achylie ou sans achylie ne se montre dans ce matériel.

Table III.

Les valeurs du fer du sérum à raison de l'achylie gastrique.

Le fer du sérum au-dessous de 60 γ %				Le fer du sérum au-dessus de 60 γ %			
Avec l'achylie		Sans l'achylie		Avec l'achylie		Sans l'achylie	
Femme	Homme	Femme	Homme	Femme	Homme	Femme	Homme
5	1	6	1	11	7	6	15

Si nous revenons aux premières courbes on voit, comme nous l'avons déjà dit, que les valeurs basses du fer du sérum sont bien plus communes chez les femmes: Dans 7 cas nous trouvons des valeurs au dessous de 50 γ % et dans 13 cas des 50 des valeurs au dessous de 60 γ %. Chez les hommes nous avons deux cas au dessous de 50 γ % et 4 cas au dessous de 60 γ %.

Aucun parallélisme entre les valeurs très basses du fer de sérum et les valeurs plus basses de l'hémoglobine ou de globules rouges du sang n'a pas pu être définitivement montré sur ce «matériel normal», ce qu'on voit par mes courbes. Ainsi j'ai trouvé, par exemple, une des plus basses valeurs du fer du sérum, 40 γ %, chez un homme, qui avait 100 % d'hémoglobine et 5.10 millions de globules rouges, et dans un autre cas chez une femme, une valeur de 37 γ % avec 80 % d'hémoglobine et 4.20 millions de globules rouges. Ces deux cas étaient de vieux hémiplegiques qui avaient été soignés longtemps pour les suites de cette maladie après un ramollissement cérébral. Dans un autre cas un homme avait une valeur relativement basse d'hémoglobine de 80 % et 4.10 millions globules rouges, alors que la valeur du fer du sérum était une des plus hautes constatées, 193 γ %.

On ne peut pas non plus constater que les plus basses valeurs du fer du sérum se trouveraient de préférence chez les plus vieux malades: dans les 11 cas au dessus de 85 ans, qui ont été examinés les valeurs sont pour les femmes (9) entre 30 γ % et 135 γ % avec 3 cas en dessous de 60 γ % (30.50 et 52 γ %) et 2 cas au dessus de 100 γ % (110 et 135 γ %), alors que les valeurs pour les 2 hommes les plus âgés sont 117 γ % et 195 γ %.

Je crois pouvoir cependant avoir prouvé que chez les vieillards, surtout chez les femmes, il y a assez souvent une sidéropénie latente de cause inconnue. Cela semble cependant ne pas avoir de rapport avec l'achylie.

II.

La sidéropénie chez des ulcères de varices aux jambes.

Depuis la fin de l'année 1942 j'ai pu rassembler un matériel de 20 cas d'ulcères chroniques de varices aux jambes chez des vieillards n'ayant pas d'autre maladie qui pouvait être soupçonnée d'avoir une influence sur la circulation du fer (tumeur, maladie contagieuse chronique, hémorragie). Dans tous ces cas l'examen a été complété par l'examen complet du sang y compris l'examen du fer du sérum et de la réaction de Wassermann. Dans l'anamnèse on a cherché après une diète pauvre en fer, et quand à cet égard on a eu le moindre soupçon ces cas n'ont pas été pris. En ce qui concerne le genre et l'aspect des ulcères ils ont été (comme

c'est le cas chez les vieillards) chroniques et récidivants, de grandeurs différentes, mais avec l'aspect caractéristique, bien limités contre la peau le plus souvent mince et de couleur brune.

Parmi 20 cas examinés il y avait 16 femmes et 4 hommes. 7 cas avait une sidéropénie manifeste, parfois avec une grave anémie. Chez 13 des 16 femmes la valeur du fer du sérum était au dessous de la valeur normale; il en était de même chez 3 des 4 hommes. Quand on examinait les valeurs du fer du sérum et du sang chez ces 20 cas d'ulcères, on pouvait faire des constatations intéressantes. Chez 7 de ces 20 cas la valeur du fer du sérum était au dessous de 40 γ %. Chez les 16 femmes 2 seulement avait au dessus de la normale, dont une avec la haute valeur de 135 γ %. Cette malade était une femme de 75 ans, qui avait été soignée auparavant, plusieurs fois, pour des ulcères aux jambes et qui une année plus tôt avait eu une anémie, traitée avec du fer. A son dernier séjour à l'hôpital, lors d'une récurrence d'ulcère à la jambe, le sang était normal et le fer du sérum était élevé. Dans 2 des cas atteints d'anémie sidéropénie la valeur de l'hémoglobine était au dessous de 50 %. L'une de ces malades est morte de marasme après 2 mois. L'autre se rétablissait; les ulcères guérissaient et l'anémie disparaissait après 6 mois avec un traitement de fer. Comme valeur moyenne pour les 16 femmes atteintes d'ulcères chroniques aux jambes on trouve une valeur de $57.7 \pm 6.29 \gamma$ % et si on exclut le cas avec la plus haute valeur on a pour les 15 autres cas une valeur moyenne de $52.5 \pm 4.23 \gamma$ %. Si on conte la différence de la valeur moyenne pour les personnes bien portantes, cette différence est dans les deux cas statistiquement établie (31.0 ± 6.23 - respectivement $25.8 \pm 7.84 \gamma$ %). Chez les malades de mon matériel, ayant des ulcères aux jambes les valeurs sont beaucoup au dessous des valeurs normales, quand il s'agit des femmes.

Chez les 4 hommes on constate dans 3 cas une valeur du fer du sérum au dessous de 50 γ %, tandis que le quatrième avait une valeur normale. Dans l'un des 3 cas il y avait une sidéropénie évidente avec anémie et 58 % d'hémoglobine; dans un autre cas une anémie avec 74 % d'hémoglobine et 35 γ % de fer du sérum. Les examens du sang et de la moelle, (quand ces examens ont pu être faits) n'ont rien montré de spécial sauf l'anémie. Dans plusieurs cas les examens du suc gastrique ont été faits, et une achylie réfractaire à l'histamine semble être assez fréquente. Comme le

matériel est trop insuffisant jusqu'à présent je n'ai pas pu faire des conclusions sûres à ce sujet. D'autres symptômes objectifs de la sidéropénie ont aussi été trouvés; mes futures recherches montreront si ces symptômes sont ordinaires ou non. On a soigné ces malades en les tenant alités, les jambes élevées, avec une diète normale, du fer en grandes doses en cas de sidéropénie (17 des 20 cas) et une thérapie locale, en général le traitement avec le fer a eu un bon résultat et a amené une rapide amélioration de l'anémie en même temps qu'une augmentation du fer du sérum à la valeur normale. Quelques cas se sont cependant montrés plus réfractaires. Dans les cas où l'anamnèse a montré une forte tendance de récidence la continuation du traitement de fer a été recommandé, même après que les ulcères ont été guéris.

Je veux aussi dire quelques mots sur les résultats du traitement. 2 femmes sur les 20 cas sont mortes. L'une avait 74 ans, avec anémie grave sidéropène et marasme, l'autre, âgée de 78 ans, est morte d'une bronchopneumonie. A l'autopsie les diagnostics ont été vérifiés et rien de remarquable n'a été trouvé au sujet de la cause de la sidéropénie. Chez 16 des 18 cas les ulcères aux jambes se guérissaient après un traitement plus ou moins long; dans les 2 autres cas on pouvait constater une sensible amélioration. J'ai trouvé intéressant d'essayer d'avoir une idée de la longueur du traitement, souvent très long chez les vieillards qui ont des ulcères chroniques aux jambes. Les cas pris dans mon matériel ont eu un traitement qui a varié entre 4 semaines et 6 mois, sauf un cas, où les ulcères ne se sont pas guéris avant un an et demi. Cette malade, âgée de 77 ans, avait une très forte artériosclérose périphérique et une atrophie de la peau. 2 de ces malades sont mortes, comme je l'ai déjà dit, toutes les deux 8 semaines après leur arrivée à l'hôpital. Pour les 17 autres cas la durée du traitement était dans 11 cas de moins de 4 mois, en moyenne 7 semaines, dans les autres 6 cas de 4 à 6 mois. Pendant l'année 1941, par conséquent avant l'introduction du traitement par le fer, 10 cas d'ulcères aux jambes sans complications étaient soignés, et ces malades avaient une durée moyenne de traitement de 34 semaines avec une variation de 14 à 96 semaines. Je cite ces chiffres comme comparaison. Ici aussi le matériel est trop petit, mais j'ai l'impression que le traitement par le fer active la guérison. En ce qui concerne mes 20 cas d'ulcères aux jambes je renvoie le lecteur à la table IV.

Table IV.

Le matériel de 20 cas d'ulcères chroniques de varices aux jambes.

Cas	Sexe	Âge ans	Ulcères depuis ans	Le fer du sérum % %	Temps de traitement	Résultat
1	Femme	65	30	72	1 mois	guérie
2	Femme	60	18	34	6 mois	guérie
3	Femme	62	$1\frac{1}{12}$	59	3 mois	guérie
4	Femme	68	$\frac{1}{2}$	53	$1\frac{1}{2}$ mois	guérie
5	Femme	70	12	69	2 mois	améliorée
6	Femme	66	$1\frac{1}{12}$	29	1 mois	guérie
7	Femme	65	$3\frac{1}{12}$	44	$1\frac{1}{2}$ mois	guérie
8	Femme	74	25	37	2 mois	morte (marasme)
9	Femme	78	10	37	$1\frac{1}{2}$ mois	morte (pneumonie)
10	Femme	80	1	54	1 ans	améliorée
11	Femme	77	$1\frac{1}{2}$	56	$1\frac{1}{2}$ ans	guérie
12	Femme	75	$2\frac{1}{12}$	135	6 mois	guérie
13	Femme	73	7	50	5 mois	guérie
14	Femme	77	1	69	6 mois	guérie
15	Femme	88	$1\frac{1}{2}$	38	4 mois	guérie
16	Femme	79	2	88	1 mois	guérie
17	Homme	68	1	142	1 mois	guéri
18	Homme	81	$1\frac{1}{12}$	35	2 mois	guéri
19	Homme	66	8	50	2 mois	guéri
20	Homme	82	5	25	$3\frac{1}{2}$ mois	guéri

Résumé.

Les ulcères des varices aux jambes du type récidivant se constatent souvent chez les vieillards en même temps qu'une anémie sidéropène et ces deux maladies semblent avoir un rapport entre elles qui n'est cependant pas encore prouvé mais qui me semble assez probable. Par l'absorption du fer on obtient, en général, une prompte réaction et les valeurs du sang et du fer du sérum montent en général rapidement. Il me semble que ce fait devrait avoir son importance pour obtenir une guérison plus rapide des ulcères chroniques aux jambes. J'ai l'intention de continuer mes recherches sur un plus grand matériel pour voir si les ulcères des varices peuvent être considérées comme un symptôme d'anémie sidéropène.

de la peau comme d'autres symptômes ectodermiques de l'anémie sidéropène, ou bien s'il y a d'autres rapports entre ces deux symptômes.

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Supravital Analysis of Disorders in the Cerebral Vascular Permeability in Man.

By

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(Submitted for publication April 28, 1944).

The theory of a blood-brain-barrier is based on the fact that certain substances are unable to pass into the brain from the blood, although they find no difficulty in penetrating into other organs. This is best demonstrated by means of special dyes, e.g. trypan blue (Goldmann, 1913; Spatz, 1933). According to recent research, the blood-brain-barrier seems to constitute a special quality of vascular permeability peculiar to the cerebral vessels (Spatz, 1933; Broman, 1940).

It can be shown in experimental animals with local cerebral lesions that, after intravenous injection of trypan blue, the brain tissue is coloured blue in the damaged area, thus demonstrating damage to the walls of the vessels with impairment of their permeability function. This method, which is known as the colour indicator method, was described in detail by the writer in papers published in 1938 and 1940.

In several morbid conditions, disorders in the permeability of the cerebral vessels may be suspected of playing a more or less significant pathogenetic role. The colour indicator method, however, was not suitable for study of this factor in man, as long as such an investigation required the injection of dyes before death. A new avenue of approach was opened by the observation in experimental animals that the permeability-regulating function of the brain

vessels did not cease with death of the individual (Broman, 1938 and 1940). This was explained as a survival of a cellular function. Thus a disturbance in the permeability function could still be demonstrated a short time after death in animals with cerebral lesions brought about *in vivo*. The vessels of the head had only to be perfused *post mortem* with a solution of trypan blue and then thoroughly washed out. The damaged parts of the brain were then found to be stained blue in the same manner as if the dye injection had been given *in vivo*.

This method of postmortal analysis with certain modifications has now for the first time been tested on human material. The brain was removed before the injection of the dye into its vessels so as to avoid discoloration of the other tissues of the head. Canulas were inserted — one in the carotid artery on one side, the other in the vertebral artery on the other side. The perfusion was performed with the brain floating in water and with a pressure of 1.0 increasing gradually to 1.3 meters of water, in order to counteract the resistance to perfusion caused by the absorption of water by the brain. The system of perfusion was as follows:

- 1) 0.2% trypan blue solution in normal saline: about 400 Ml/10 min.
- 2) Normal saline : » » » / » »
- 3) 5—15 % formaldehyde solution : » » » / » »

The thoroughness of the perfusion was tested in two ways: Firstly by control of the fixation and secondly by microscopic study of the blood vessels. If the perfusion was satisfactory, frozen sections of the brain could be made immediately afterwards and the vessels were found to contain only few blood corpuscles.

The material comprises 13 cases from the Neurological and the Neurosurgical Departments of the Serafimer Hospital, Stockholm, and was kindly put at my disposition by the heads of the departments, professors N. Antoni and H. Olivecrona, to whom I would express my grateful thanks. The investigation was carried out at the Brain Laboratory of the Neurological Department, where space and equipment were made available to me through the kindness of professor Antoni.

As appears from table 1, the perfusion must be started within a few hours after death if a satisfactory result is to be obtained. Later on there is found diffuse staining of the whole brain, due to postmortal cessation of the permeability function and to incom-

plete washing-out of the dye in consequence of pronounced resistance to the perfusion in these cases (autolysis of the brain with swelling during the perfusion?), the same factor being responsible for the defective fixation.

Table 1.

Relation between the interval from death to perfusion and the results obtained.

Perfusion begun					No. of cases	Fixation	Diffuse staining of whole brain
About	1 hour	post mortem			5	+	—
"	1 ½	"-5	"	"	3	+	—
"	2	"	"	"	3	(+)	—
"	8	"	"	"	1	—	+
"	10	"	"	"	1	—	+

After elimination of the two cases with diffuse staining of the brain, there remain 11 technically successful ones, some of which exhibit more than one lesion of interest in this connection. The findings can be summarized as follows:

Table 2.

Nature of lesion	No. of observations	Results
Malignant glioma	3	Staining of non-necrotic parts of tumor
Cerebral astrocytoma	2	" " the tumor
Melanosarcoma	1	" " " "
Benign cyst of the septum pellucidum	1	No staining of wall of cyst
Encephalomalacia	1	Perifocal staining
Cerebral hemorrhage	1	" "
Edema	4	Staining of the edematous regions
Ventricular puncture canal	1	" " wall of canal
Abscess	1	" " " abscess
Multiple Sclerosis	1	" " demyelinated areas

Special attention should be paid to the cases of tumor, edema and multiple sclerosis.

As to the tumors of the brain, their vessels seem to lack the special permeability function of the blood-brain-barrier, a fact that may be of interest to further research on the morphological or

physicochemical basis of the barrier. The abnormal permeability of the glioma vessels perhaps also is responsible for the tendency to cyst-formation exhibited by these tumors — an explanation, however, that does not hold true in the case with a benign cyst.

In the hope of turning this peculiarity of the cerebral tumors to clinical advantage, an investigation was started in cooperation with a chemist (S. Sunner) and a roentgenologist (S. Eriksson). Certain substances resembling trypan blue in structure, but containing iodine, were administered by intravascular injection to animals with cerebral lesions, in order to render the damaged areas radiographically visible. The compounds tested, however, turned out to be unfit for the purpose, as their opacity to X-rays was too low in relation to their toxicity and their degree of solubility.

In the cases of cerebral edema, the edematous condition of a hemisphere or part of it was obvious before perfusion and could not, therefore, be attributed to postmortal absorption of fluid. Good fixation and microscopic control also proved that no dye had stagnated in the vessels. As it is a generally accepted fact (Haller-vorden, 1940; and others) that the myelin becomes more or less destroyed in regions affected with cerebral edema, myelin-stained preparations were examined. First it was shown that postmortal staining of brain sections with trypan blue did not hamper subsequent myelin staining. When the edematous regions were investigated, it was found that the distribution of the dye exactly corresponded with the varying degree of demyelination. Here therefore is a strong argument for the assumption that the penetration of the dye during the postmortal perfusion is actually caused by a disorder of the vascular permeability already present *in vivo*. The results suggest that a disturbance in vascular permeability is the main factor in the development of cerebral edema, even if local metabolic disorders in the brain and irregularities in the general fluid balance of the body are factors which also should be taken into account as contributory causes.

Outside the edematous regions and in some other cases without gross edema but in which an increased intracranial pressure might have been at least a contributory cause of death, blue-stained, subcortical areas of varying size were found, which at first were considered to be artefacts. In myelin-stained sections these areas showed the same correspondence between blue-staining and demye-

lination. These foci were, therefore, interpreted as signs of beginning edema, still localized in scattered areas.

The clear connection between a permeability disorder and demyelination (the relationship of the trypan blue preparations to the myelin-stained ones was as positive to negative) is an observation which also adds interest to the final problem, as follows.

In the case of multiple sclerosis (the disease history was very short — only about six months), the demyelinated areas exactly corresponded with a disturbance of the vascular permeability, e.g. the blue-staining increased with the degree of demyelination both in different areas and in different parts of the same area.

The most important question to arise concerns the causality. Is the demyelination to be regarded as a primary, secondary or parallel phenomenon to the disorder in permeability? This question will be studied in greater detail at some later date, but there is one point which can be made at this time: in the case of cerebral edema the disturbance of permeability is likely to be primary in relation to the edema, which in some way leads to demyelination. It may be that the same also applies to multiple sclerosis.

Summary.

Damage to the walls of the cerebral vessels with impairment of their permeability function may be demonstrated with a colour indicator method a short time after death. This method has now for the first time been tested on human material. After removal of the brain its vessels were perfused with a solution of trypan blue.

Eleven technically successful cases (perfusion within a few hours after death) were investigated. Disorder of the barrier function could be demonstrated in malignant glioma, astrocytoma, melanosarcoma, encephalomalacia, hemorrhage, edema, abscess and multiple sclerosis.

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On Serum Copper. I. Introduction.¹

By

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(Submitted for publication February 25, 1944).

Not till recently has copper been proved an indispensable element in the animal organism. It was Me Hargue (15) who started investigations into this question, and in 1928 Hart, Steenbock, Elvehjem and collaborators (9) in experiments on rats and subsequently on mice, rabbits, dogs, swine and chicken demonstrated the necessity of copper for the normal synthesis of hemoglobin. These experiments have been reviewed and discussed by Ege (5). Elin Fog (6) has shown that the copper deficiency anemia in rats is microcytic. As early as 1931 veterinarians (17) pointed out the existence of a special copper deficiency disease, which occurs spontaneously in cattle, sheep, goats and swine in various parts of the world (22, 4). In cattle this disease manifests itself by anemia, emaciation, diarrhea and interrupted capacity for breeding; and the animals will die of this disease if they are not transferred to »healthy» pastures or supplied artificially with iron and copper salts. Innes (12) has studied this lesion especially in sheep, and Bennetts & Chapman (2) demonstrated that it is due to copper deficiency. In sheep this form of anemia is characterized by being macrocytic, and the lambs of such sheep are attacked early by an ataxia that leads to the death of the animal within a short time.

¹ On Serum Copper. II will be published in *Acta physiologica scandinavica*.

So far it has not been possible in man to demonstrate similar clinical features brought about by copper deficiency. Only during the first months of life is the diet so poor in copper that copper deficiency due to an inadequate supply seems possible. The amounts of copper required by the human organism are very small, however, and most likely this is the reason why the pediatricians (10, 11, 13) do not agree on the necessity of copper therapy together with iron treatment in infantile anemia. The clinicians further differ in their opinion about copper deficiency from absorptive disturbances in adults, some authors (20, 16) claiming that certain anemias are not cured completely without an addition of copper to the iron therapy, while others (8, 3) assert that copper has no therapeutic effect whatever. On the other hand, investigations by means of the more recent methods of quantitative copper determinations on the serum of human subjects, both normal and patients with various diseases, have shown that significant variations in the serum copper concentration occur under both physiological and pathological conditions. The progress made in the technique of these determinations may be illustrated appropriately by the fact that Abderhalden & Møller (1) in 1928, using classical methods, had to employ 1 liter of serum for their analysis, whereas now 1 ml is sufficient. This progress is due to the introduction of various highly-coloured copper compounds and their colorimetry (21, 14, 19), or special arrangements as used by O. Warburg (23) or Guillemet (7). The method of McFarlane (14), based upon the very strong colour-reaction between copper and diethyl-dithiocarbamate, appears to be superior to the other substances which so far have been tried. The modification employed by the author will be described in detail in a subsequent report. (18)

It may thus be evident that the copper metabolism of the human organism involves several problems worthy of investigation. The subsequent papers of this series will contain reports of the author's investigations in some of these fields.

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On Serum Copper. III. Normal Values.

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Owing to the analytical difficulties, so far only a few investigations have been reported on variations in the serum copper concentration under normal and pathological conditions. As normal values, obtained with earlier methods, O. Warburg (11) gives 124 γ %, and Sarata (9) gives 33—63 γ %, while the values given by other authors lie at entirely different levels and hence will not be discussed here.

With various modifications of the thiocarbamate method, normal values of about 200 γ % were obtained by McFarlane (5) and by Tompsett (10), whereas Locke *et al.* (4) found an average value of 80 γ % for 8 men and 92 γ % for 9 women; the apparent sex difference, however, may be due to random sampling. Heilmeyer *et al.* (2) (1941) found 106 γ % as the normal value, the same for 30 men and 30 women with a range from 70 to 140. From the data recorded it is not evident, whether or not all the experimental subjects were fasting. Sachs *et al.* (8) (1941) found 105 γ % for 10 men, varying from 84 to 132; and Braun & Scheffer (1) (1940) give 119—157 γ % as normal values, without stating whether they are fasting values.

My material comprises 100 normal women, from 18 to 48 years old, and 30 normal men, aged 17 to 38. They have all been feeling well, *i. e.*, able to work, free from infection and presenting no

abnormality on ordinary clinical examination, including the sedimentation test. All the blood samples were taken in the forenoon, one or two hours after breakfast. All the analyses were carried out in duplicate, and in no instance did the difference of the results exceed 4 %, while as a rule it was 1 % or less. The analytical method followed has been reported elsewhere in detail (6). The results are recorded graphically in Fig. 1.

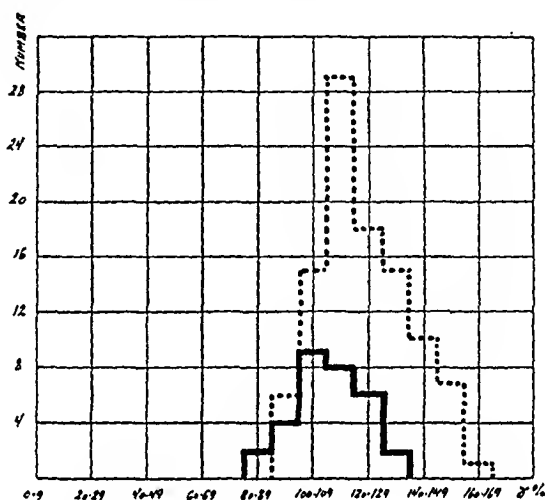


Fig. 1. Serum copper in 100 normal women . . . , in 30 normal men —.

Although both curves are apparently skew, with a more protracted fall to the right, a test with the probit method shows that they are suitable for statistical treatment as in normal distribution of the values. The mean for women is 123, 15 γ % ($s = \pm 16.24$), for men 110.53 γ % ($s = \pm 12.14$). The difference between these two means is significant, (exceeding the 0.1 per cent level, $t = 3.86$) indicating a real sex difference. This is in conflict with the results obtained by Heilmeyer (2); it may perhaps be connected with the lower serum iron concentration in women, since an apparent antagonism between serum iron and serum copper has been demonstrated often (7, 3), and usually the deviations from the normal have gone in opposite directions. Considered as a total, the upper and lower 1 per cent limits for serum copper in normal, non-fasting individuals will be $123.15 + 16.24. 2.58 \gamma$ %, i. e. 165.04 γ % and $110.53 + 12.14. 2.756 \gamma$ %, i. e. 77.08 γ %, or more practically 165 and 75 γ %.

Before we make use of these normal values, we shall have to know a little about physiological variations: diurnal variations from work and intake of food, variations from day to day in the same individual, and in the case of women, also possible variations in relation to menstruation and pregnancy.

Heilmeyer (2) appears to be the only investigator who has looked into the diurnal variation, which he found to amount to up to 30% of the initial value. In order to throw some light on this question, I have taken samples of blood from 3 healthy subjects 5 times within 24 hours. At 6.30 the subjects were fasting and under basal conditions.

Table 1.

Diurnal Variations in Serum Copper in Normal Subjects.

	Hour	6.30	11.30	14.00	17.00	22.00
1. Male, aged	35	104	109	110	105	114
2. Male, aged	31	70	90	90	84	107
3. Female, aged	29	103	111	110	110	125

From Table 1 it is evident that the diurnal variations in serum copper may be quite considerable; in all three persons the fasting value is the lowest. The latter point is further evident from the fact that no value as low as 70 is found in the author's normal material from non-fasting individuals.

Variations in serum copper from day to day have been examined in altogether 6 samples of blood taken from each of 5 normal women within a period of about 15 days. The findings are presented graphically in Fig. 2.

During the observation period, menstruation appeared in 3 of these 5 women, without having any demonstrable influence on the

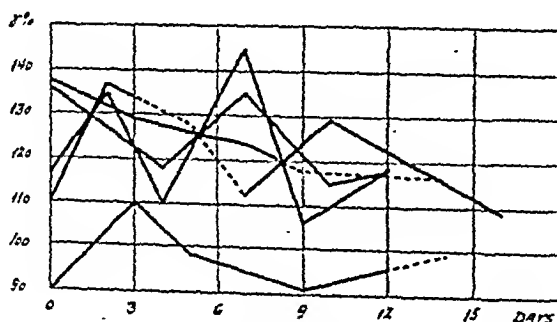


Fig. 2. Serum copper on various days in 5 normal women.
Period of menstruation

variations in serum copper. That menstruation has no influence on the serum copper concentration has been stated previously by Locke *et al.* (4) and by Heilmeyer *et al.* (2), whereas Sarata (9) found the values for serum copper to be much higher just before the menstruation than after. By plotting the serum copper values for all the normal women in a coordinate system in relation to the last menstrual period, the menstrual cycle has been found to give no variation in serum copper. A corresponding plotting of the values after the age of the individual subjects shows that the serum copper concentration keeps the same level from the menarche to approaching menopause. On the other hand, very pronounced changes in the serum copper concentration are observed during pregnancy (as will be demonstrated in detail in the subsequent paper).

When the normal samples were collected, 6 women stated they had a «cold» or sore throat. Nevertheless, 3 of these women showed a normal sedimentation rate and normal serum copper values. In the remaining 3 women the findings were as follows:

	Cu γ %	S.R. mm, 1 hour	Cu γ %	S.R. mm, 1 hour	Cu γ %	S.R. mm, 1 hour
1. B.	175	5	125	4 (4 weeks later)		
2. O.	224	7	151	16 (6 " ")	177	15 (5 months later)
3. N.	159	22	170	18 (7 " ")		

From the findings on reexamination of these women it seems most probable that while No. 1 soon was well again, the two others had acquired some more protracted latent infection.

In addition, 2 women showed an increase in serum copper (232 and 200 γ %), with normal sedimentation rate and no clinical symptoms, and on repetition of the examination 3 weeks later, they showed normal values for serum copper. In these two cases more likely the high copper values obtained in the first test were attributable to a technical error, brought about by the employment of bi-distilled water from a flask provided with rubber tubing, as rubber tubing contains copper.

One woman, who had no «cold», showed a sedimentation rate of 22 mm and a serum copper concentration of 152 γ %. One month later the sedimentation rate was 16 mm, serum copper 161

γ %; 2 weeks later, S.R. 20 mm; and 5 months later, S. R. 10 mm, and serum copper 158 γ % — that is, a rather high normal value.

These examples illustrate how readily a slight infection may be associated with a marked increase in serum copper and that the serum copper concentration may be even more labile than the sedimentation rate, returning to a normal level more slowly.

Summary.

A brief review is given of previous reports on the serum copper concentration in normal persons.

In 100 normal, healthy, non-fasting women, the writer found 123 micrograms of copper per 100 ml of serum with a standard deviation of 16 micrograms, in 30 normal men 110 micrograms of copper with a standard deviation of 12 micrograms. The limits for normal values for serum copper in adult, non-fasting persons are 75 and 165 γ %.

It is further shown how the serum copper concentration in the same person is subject to considerable diurnal variation as well as to variations from day to day, though not outside the given limits, the fasting value excepted.

It is finally shown that the menstruation has no influence on the serum copper concentration, whereas this may be affected markedly by infections.

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On Serum Copper. IV. Pregnancy and Parturition.

By

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(Submitted for publication February 25, 1944).

In 1928 Krebs (2) demonstrated that the serum copper concentration is considerably increased during pregnancy, and later this was confirmed by Schindel (9), Lucke *et al* (4), Sarata (8), Lesné *et al* (3) and Norinder (6), employing various microchemical methods for the determination of copper. The absolute values for copper given by these authors differed somewhat, however, and Sarata (8) thought that the rise in serum copper is present only during the first part of pregnancy, whereas Lesné (3) asserted that it was present till the parturition. After examination of 10 pregnant women Heilmeyer *et al*. (1) arrived at the conclusion that serum copper is particularly increased towards the end of pregnancy, and they suggested that the serum copper determination might be used as a diagnostic adjuvant early in pregnancy.

For the sake of further elucidation of this question, the author has estimated the serum copper concentration in 31 pregnant women and 41 parturients. The method of analysis is the same as has been mentioned and described in a previous paper (5)¹. The patients were never fasting when the sample of blood was taken. All the pregnant women were consulting the out-patient depart-

¹ All the analyses were made in duplicate and the difference of the results did not exceed 3 %.

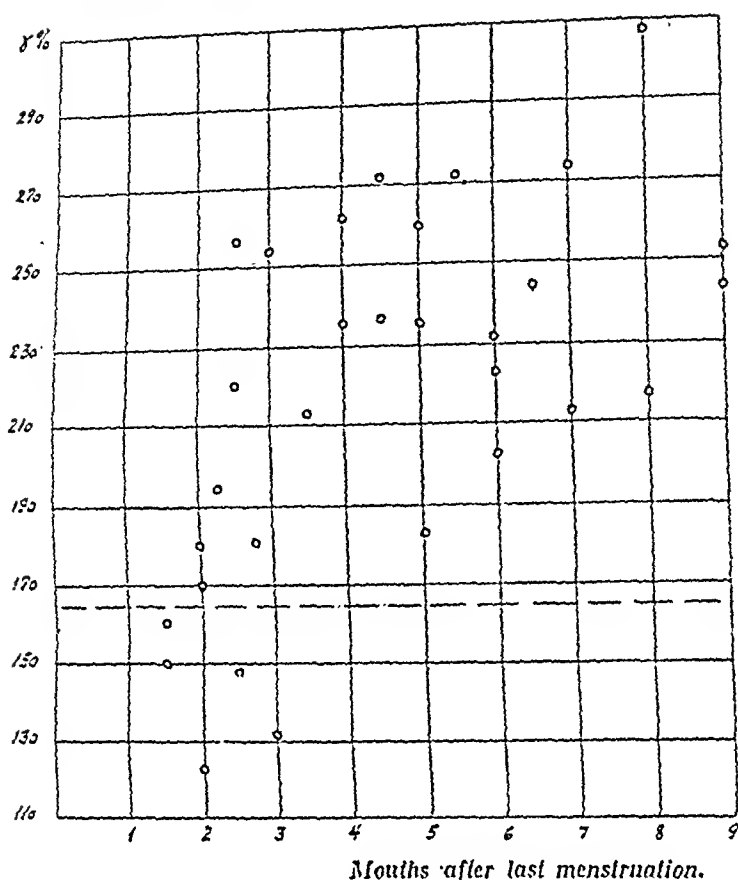


Fig. 1. Serum copper during pregnancy. (Upper normal limit: 165 γ %).

ment; 7 sought advice for dyspepsia, lipothymia, etc. and presented merely pregnancy as explanation of their complaints; the others were referred to the clinic for the sake of observation for cardiac disease (which could be demonstrated only in 2 out of 13 cases), glycosuria in pregnancy, goiter, or — what most often was the case — for the sake of thorough medical examination in order to be taken in for delivery in the hospital. At the time of their examination none of the patients included in the present material had a cold or albuminuria, hyperthyroidism or other conditions known to be associated with a rise in serum copper. The parturients were patients picked out at random on four days in November 1942 and four days in March 1943. Of these patients 4 had to be excluded from this material: 2 with syphilis, one with open pulmonary tuberculosis, and one with eclampsia. On most of them

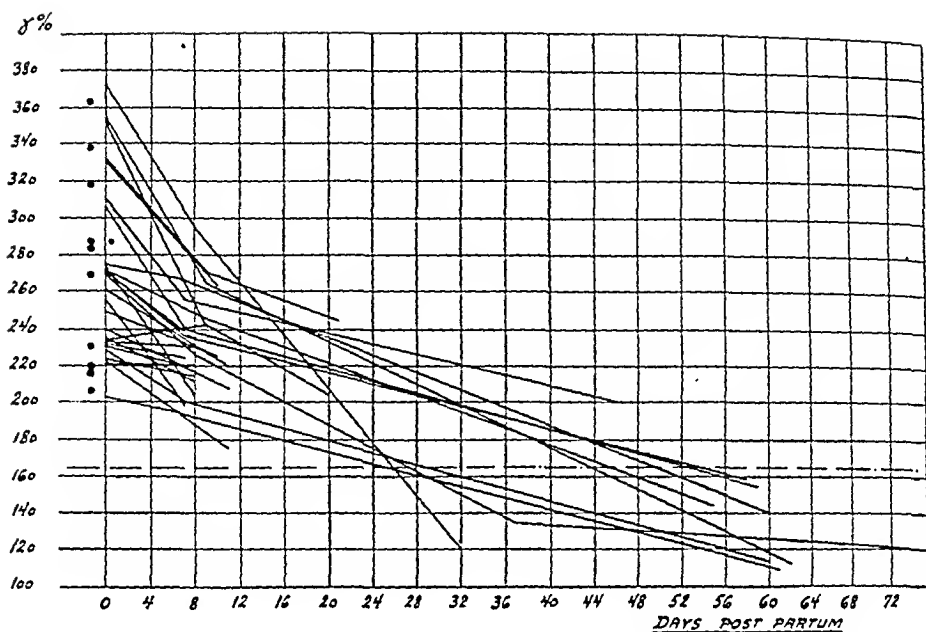


Fig. 2. Serum copper at the parturition, in the puerperium and labor. (The first row of points represent parturients in whom this was the only analysis performed).

the test was repeated shortly before their discharge, but 3 had to be ruled out on account of fever in the puerperium (Pyuria, Phlebitis). Thus this material includes 37 analyses from the day of delivery, 27 from the end of the puerperium and 10 from an additional test, performed a few weeks after the parturition.

From Fig. 1, which shows the outcome of the serum copper determinations in the 31 pregnant women, it is plainly evident that in the first three months of pregnancy the serum copper values sometimes fall within the normal limits (up to 165 γ %), sometimes are increased, and only after the third month are all of them increased. This abolishes any possibility of an early diagnosis of pregnancy by means of serum copper determination.

Fig. 2 illustrates the serum copper concentration at delivery and shortly after. Even a few days after labor the fall in serum copper towards normal level is distinct; 4—7 weeks after parturition 9 out of 10 patients showed normal values. At that time, the one patient, in whom the serum copper was still increased, gave a sedimentation reaction of 22 mm, without presenting any other

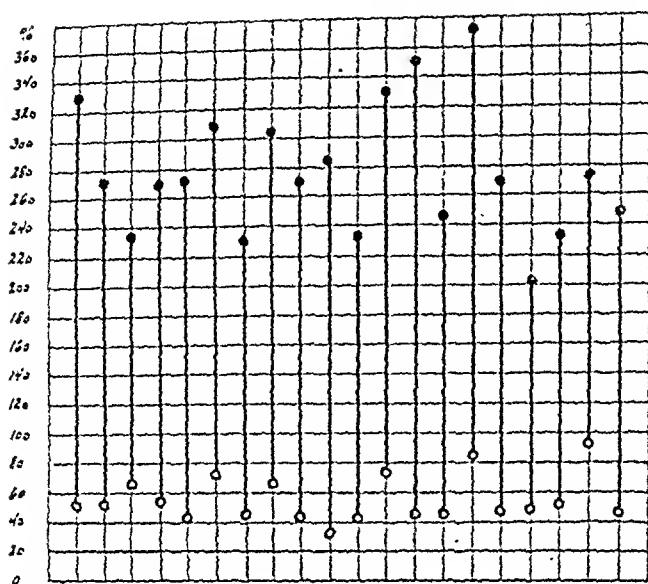


Fig. 3. Serum Copper Values in Mother • and Child ○.

reason for this phenomenon besides the puerperium. In 37 patients the analyses showed an average serum copper concentration of $269.6 \gamma \%$ with a standard deviation of $\pm 48.03 \gamma \%$.

At the same time as the maternal serum copper was determined, in 20 cases another copper determination was carried out on serum derived from umbilical cord blood. Already Schindel (9), Locke *et al.* (4) and Lesné *et al.* (3) found the copper concentration to be much lower in fetal serum than in the maternal serum; and Sachs *et al.* (7) found very low values for the copper content of whole blood from the umbilical cord.

The writer is able fully to confirm this striking difference in the blood of the mother and the child — as shown in Fig. 3.

The average value for the children is $55.7 \gamma \%$, but it is to be pointed out that one half of the specimens gave values under $50 \gamma \%$. If, in spite of this skewness in the dispersion of the values — which was present too, although less pronounced, in the material of adult women and men — we calculate the standard deviation for these values after the usual formulae, it is found to be $\pm 15.64 \gamma \%$.

Summary.

In analyses on 31 pregnant women the serum copper is found as a rule to be increased from the third month of pregnancy. At delivery, 37 parturients showed an average serum copper concentration of 269 γ % (standard deviation ± 48.03 γ %). In the umbilical cord blood from 20 children the copper content was much lower, averaging 55.7 γ %. During the puerperium the serum copper concentration commences to fall, reaching a normal level in a few weeks.

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Über die Nierenveränderungen bei tödlicher Sulfathiazolschädigung.

Von

HILDING BERGSTRAND.

(Bei der Redaktion am 15. April 1944 eingegangen).

Eine Reihe von Autoren haben Nierenkomplikationen bei der Sulfathiazolbehandlung beschrieben, welche von Hämaturie, Oligurie, Reststickstoffsteigerung und — bei den schwersten Fällen — Tod infolge von Urämie gekennzeichnet werden. Die erste Mitteilung über das Aussehen der Nieren bei einem derartigen Fall wurde 1940 von Horack erstattet, der Konkremeute von Sulfathiazolkristallen in den Sammelrohren und im Nierenbecken sowie intra- und extratubuläre Blutungen im Nierenparenchym fand. Zwei Jahre später veröffentlichte Lederer vier, Merkel und Crawford vier sowie Winsor und Burch drei Fälle, welche pathologisch-anatomisch untersucht werden konnten. Bei sämtlichen Fällen bestanden herdförmige Nekrosen und Blutungen in den Nieren, bei mehreren auch Nekrosen in anderen Organen, wie Leber, Lungen, Milz, Lymphdrüsen, Pankreas, Nebennieren und Knochenmark. Nekrosen in diesen letzteren Organen kamen jedoch nicht regelmässig vor. In Schweden hat *Blenda Wird* über einen tödlich verlaufenen Fall mit Obduktion berichtet, bei welchem die Nieren Anzeichen einer Nephrose von dem bei Hg-Vergiftung gewöhnlichen Typus erkennen liessen. Im Krankenhaus Sabbatsberg sind im Laufe einiger Monate sieben Todesfälle infolge von Sulfathiazolschädigung der Nieren vorgekommen; bei allen diesen Fällen wurde das gleiche, sehr charakteristische Bild gefunden, wie es im folgenden beschrieben werden wird.

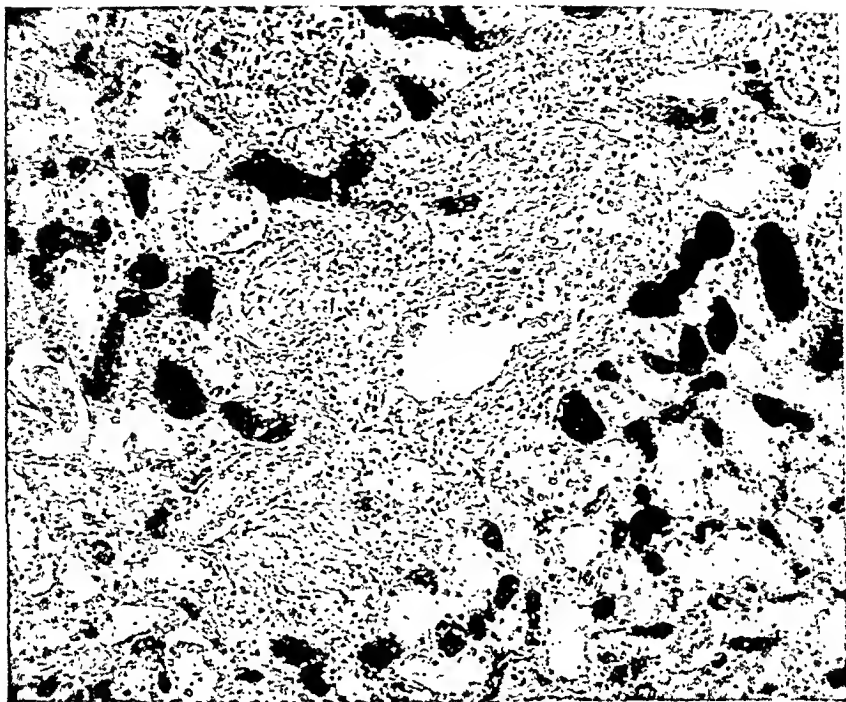


Abb. 1. Partie in der Rinde, wo die Kanälchen zugrunde gegangen sind und das Gewebe mit Rundzellen infiltriert ist. Zentral sieht man die Reste eines Kanälchens. In der Umgebung des Herdes starke Hyperämie.

Fall 1.

Obd. 30/44. ♀, 32 J. Hatte seit vielen Jahren an schwerer Mitralklappenstenose und -insuffizienz gelitten. War am 25. 12. 43 unter Fieber erkrankt, am 27. 12. aufgenommen worden und am 18. 1. 44 ad exitum gekommen. Hatte während der Zeit 2. 2.—3. 2. 42 Hallusan 16 g erhalten, 4. 2.—7. 2. 42 Sulfathiazol 10 g, 1. 7.—5. 7. 43 Sulfathiazol 26 g, 13. 10.—16. 10. 43 Sulfathiazol 24 g, 27. 12. 43—2. 1. 44 Sulfapyridin 25 g sowie 6 g Sulfapyridin in Form von Suppositorien. Folgende Rest-N-Werte sind im Krankenblatt vermerkt: 28. 12. 43: 33, 4. 1. 44: 113, 7. 1.: 176, 11. 1.: 174, 13. 1.: 156 und schliesslich 17. 1.: 146. Die Urinmengen waren anfangs sehr klein, stiegen aber während der letzten Zeit der Krankheit. Am 10. 1. war die Urinmenge 1400, am 13. 1. sogar 2400.

Pathologisch-anatomische Diagnose: Endocarditis peracta cum stenosis et insuff. grav. valv. mitral. + Cicatrices myocardii, renum et lienis + Bronchitis mucopurulenta + Atelectasis et oedema pulmonum + Infarctus renis dextr.

Die Nieren wogen zusammen 525 g. Oberfläche bis auf vereinzelte kleine, trichterförmige embolische Narben recht glatt. In der rechten Niere ein grosser, frischer anämischer Infarkt mit hämorrhagischer Randzone.



Abb. 2. Strahlenförmige Eiweissniederschläge um ausgelaugte Kristalle auf der von Epithel entblösten Oberfläche des Nierenbeckens.

In beiden Nierenbecken etliche kleine Konkreme, welche sich bei chemischer Untersuchung als Sulfathiazolkristalle erwiesen.

Mikroskopische Untersuchung der Nieren: Die Nierenarterien zeigen keine Veränderungen. In sowohl dem Mark wie der Rinde findet man zahlreiche kleine Partien, in welchen die Nierenkanälchen verschwunden oder zerfallen sind, so dass nur noch Reste derselben vorhanden sind (Abb. 1). Diese Herde sind mit Rundzellen infiltriert. In einem Teil derselben sieht man Klumpen von hyalinen Bändern und Schollen, welche sich bei *van-Gieson*-Färbung gelb und bei *Mallory*-Färbung blau färben. Rings um die Herde sind die Gefässe stark ausgespannt und mit Blut gefüllt. Hochgradige Hyperämie auch in den Nierenpapillen. Die Kanälchenepithelien lassen keine Verfettung oder Degeneration in Form hyaliner Tröpfchen erkennen, sind aber angeschwollen und weisen eine gesteigerte Körnung auf. Die Lumina der gewundenen Kanälchen sind mit einer körnigen oder faserigen Masse gefüllt, welche sich bei *Mallory*-Färbung schwach blau, bei Färbung nach *van Gieson* schwach gelb färbt. Die Ductuli papillares sind etwas erweitert. Die Glomeruli sind im grossen und ganzen unverändert; in einigen bemerkt man jedoch geronnene, schwach gefärbte Massen im Hohlraum der Bowmanschen Kapsel.

Im Nierenbecken sind die Epithelzellen stellenweise abgestossen, wobei eine hyperämische Fläche entblösst wird. Auf derartigen Flächen fin-

Datum	Flüssigkeits- zufuhr per os	Flüssigkeitszu- fuhr intravenös	Urinmenge	Sulfathiazol g	Rest-N	Sulfathiazol- kristalle im Urin	Alkalireserve	BHCO ₂	Etweiss im Urin	Reaktion des Urins	Rote Blutkör- perchen im Urin
4. 11.			800							alk.	
5. 11.			1200	36	6						
6. 11.			1400		5						
7. 11.			1600		5						
8. 11.			1800		5						
9. 11.			100+	36	5	0			+	sauer	
10. 11.	1700	1650	210+								
11. 11.	1050	2800	200	100							
12. 11.	1400	450	200	116		0					
13. 11.	875	500	180	112							
14. 11.	780	500	40	220					+	sauer	
15. 11.	325	2100	150	198		0	28	11,5	+	sauer	++
16. 11.	375	2200	255	232			33	11,5	+	sauer	
17. 11.	373	2000	300	212			37	15			
18. 11.	375	2400	160	228			43	18			
19. 11.	250		244				38	16			

Abb. 3. Obd. 312/43.

det man vereinzelte strahlige Körper, welche sich bei *van-Gieson*-Färbung gelb, bei *Mallory*-Färbung blau färben (Abb. 2). Im Hilusfett erhebliche Rundzelleninfiltration. In Gefrierschnitten von formalinfixiertem Material sieht man keine Kristalle.

Fall 2.

Obd. 312/43. ♂, 53 J. Am 14. 10. 43 wegen Prostatabeschwerden aufgenommen. 19. 11. Exitus.

4. 11. Operation Transvesikale Prostatektomie.

In der Zeit 24. 10.—9. 11. hatte Pat. insgesamt 81 g Sulfathiazol erhalten. Am 9. 11. sank die Urinmenge, welche bis dahin normal gewesen war, auf 100 g. S. auch Tab. Abb. 3.

Patholog'sch-anatomische Diagnose: Status post prostatektomiam.

Die Nieren wogen zusammen 450 g. Sie waren mit Blut strotzend gefüllt, und auf der Schnittfläche traten zahlreiche kleine Blutungen hervor. In beiden Nierenbecken fand man eine grosse Anzahl von kleinen gelblichen Konkrementen, welche, wie die chemische Untersuchung ergab, aus Sulfathiazol bestanden. Beide Harnleiter waren ausgespannt und an ihrem Durchtritt durch die Blasenwand mit Pfropfen von gelblichen Massen verstopft, welche denjenigen im Nierenbecken glichen (Abb. 4).



Abb. 4. Längliche Konkreme in den Ureteren an deren Eintritt in die Blase. Die Harnleiter sind erweitert.

Mikroskopische Untersuchung der Nieren: Arteriosklerotische Veränderungen sind nicht zu konstatieren, ebensowenig Verfettung oder Degeneration in Form hyaliner Tröpfchen in den Kanälchenepithelien. In den Lumina der gewundenen Kanälchen ein dünnes Netzwerk einer schwach färbbaren Masse. Ductuli papillares nicht erweitert. Sowohl im Mark wie in der Rinde findet man verstreut stark hyperämische Gebiete mit Blut in den Kanälchen. Namentlich im Anschluss an diese, aber auch an anderen Stellen, sind innerhalb kleiner Partien die Kanälchen verschwunden. Statt der letzteren sieht man Rundzelleninfiltrate und kleine Klümpchen von hyalinen Bändern und Schollen (Abb. 5). Zwischen diesen liegen Rundzellen oder vereinzelte Epithelien der zerstörten Kanälchen. Die Klümpchen, welche ungefähr ebenso gross sind wie ein Glomerulus, färben sich bei Mallory-Färbung blau und bei van-Gieso färbung gelb. Sie geben mithin nicht die Fibrinreaktion. In gewissen Klümpchen werden jedoch einige Stücke der Bänder bei Mallory-Färbung rot. Die vorstehend beschriebenen Herde, deren Aussehen sehr charakteristisch ist, kommen sowohl im Mark als auch in der Rinde vor. Die Glomerulusschlingen sind stark mit Blut gefüllt. In den Kapselräumen geronnene Massen, welche bei Malloryfärbung ungefärbt bleiben. Im Nierenbecken bemerkt man Blutungen in die Schleimhaut, deren Epithelien in grossen Gebieten abgestossen sind. Sonst weist die Nierenbeckenwand eine mässige Leuko-

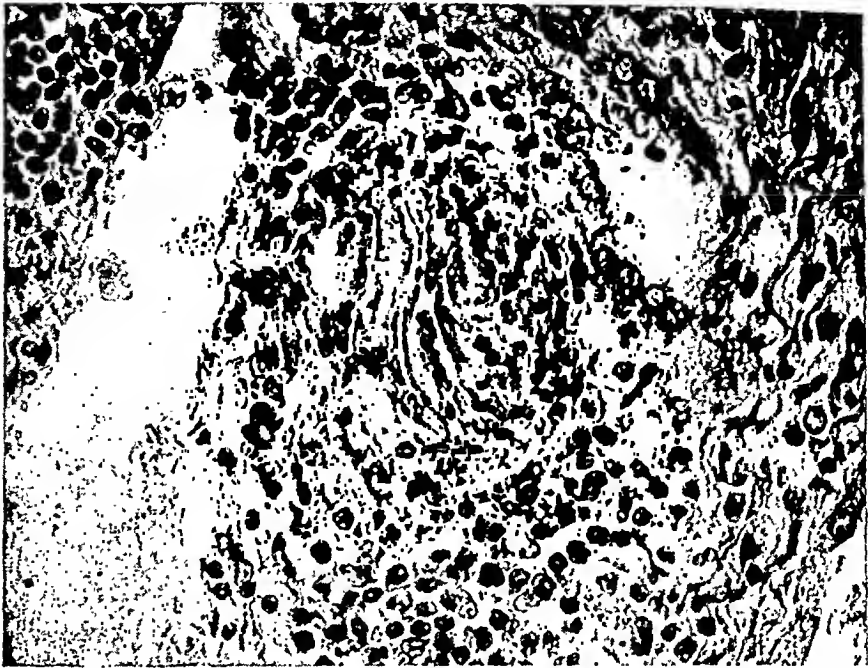


Abb. 5. Rundzelleninfiltrate mit Konglomeraten von hyalinen Schollen und Bändern.

zyteninfiltration auf. Ferner sieht man eine starke Leukozyteninfiltration im Hilusfett, und hier haben sich an mehreren Stellen kleine Abszesse gebildet. Sulfathiazolkongremente sind nicht zu finden.

Fall 3.

Obd. 340/43. ♀, 50 J. Erkrankte am 24. 11. an rechtsseitiger Lungentzündung und kam am 10. 12. ad exitum. Klinische Diagnose: Pneumonia dextr. + Uraemia. Am 4. 12. hatte die Patientin über Schmerzen in den Seiten geklagt, und es war da ein kleinmakulöses Hautexanthem beobachtet worden. S. auch Tab. 6.

Pathologisch-anatomische Diagnose: *Pneumoni. subacuta pulmon. dextr.*

Die Nieren wogen zusammen 410 g. Die Nierenbecken waren hyperämisch und enthielten eine schwarzbraune Flüssigkeit, in welcher stecknadelkopfgrosse, braune, weiche Kongremente gefunden wurden. Ureteren erweitert, kleinfingerdick. Sie enthielten ähnliche Kongremente und Flüssigkeit wie die Nierenbecken. Die chemische Analyse dieser Flüssigkeit ergab 46,5 mg % Sulfathiazol. Harnblase leer. In die Harnleiter liessen sich leicht Sonden einführen.

Mikroskopische Untersuchung der Nieren: Mässige Elastikahyperplasie in den Art. interlobularen, aber keine arteriosklerotischen Veränderungen. In sowohl dem Mark wie der Rinde finden sich hyaline Klümpchen von

Datum	Flüssigkeitszufuhr	Glykose per rectum	Urinmenge	Rest-N	Sulfathiazol g	Sulfapyridin	Sulfakonzentration im Blut	Eiweiss im Urin	Rote Blutkörperchen im Urin	Weisse Blutkörperchen im Urin	Reaktion des Urins	Kristalle im Urin
24. 11.					4							
25. 11.	2100		300		14			Spur	+	+	sauer	+++
26. 11.	1600		600		12							
27. 11.	2300		500		12		4,25					
28. 11.	2250		800		9							
29. 11.	1500		650	27	9		5	0	+	++	neutr.	+++
30. 11.	2250		600		12							
1. 12.	1800		400		8		3,75					
2. 12.	1950		1300			4						
3. 12.	1600		800			14	2,5	Spur			sauer	+++
4. 12.	600		0					+	+++	+++	sauer.	
5. 12.	1650		300									
6. 12.	350		110	71			3,4	+	+++	+++	sauer	+++
7. 12.	1900	950	20	118								
8. 12.	300		0	128								
9. 12.	950	900	0	172								
10. 12.				188								

Abb. 6. Obd. 340/43.

ungefähr Glomerulusgrösse. Dieselben sind aus hyalinen Bändern und Schollen zusammengesetzt, zwischen welchen man hier und da Reste von zerfallenen Kanälchenepithelien sieht (Abb. 7). Die Epithelien der gewundenen Kanälchen zeigen keine Degeneration in Form hyaliner Tröpfchen und keine Verfettung. Im Lumen derselben bemerkt man ein dünnes Netzwerk einer schwach gefärbten Masse. Sammelröhrchen und Ductuli papillares nicht erweitert. Die Glomeruli sind intakt. Man findet zahlreiche kleine hyperämische Herde im Mark und der Rinde sowie im Anschluss an diese Blutungen in die Kanälchen. Im Nierenbecken ist das Epithel zum grössten Teil abgestossen. Auf der entblössten Oberfläche liegen in einzelnen Schnitten rundliche, radiär-gestreifte Körper, welche sich bei *Mallory*-Färbung blau färben. Zwischen den feinen Streifen sieht man Lücken, wie nach Auslaugung von Kristallen (Abb. 8). Im Bindegewebe im Nierenbecken und ausserhalb desselben perivaskuläre Rundzellen- und Leukozyteninfiltration (Abb. 9). Die Wandungen der Venen lassen Anzeichen einer Schädigung erkennen, sie sind teilweise hyalinisiert und färben sich bei *van-Gieson*-Färbung gelb, bei *Mallory*-

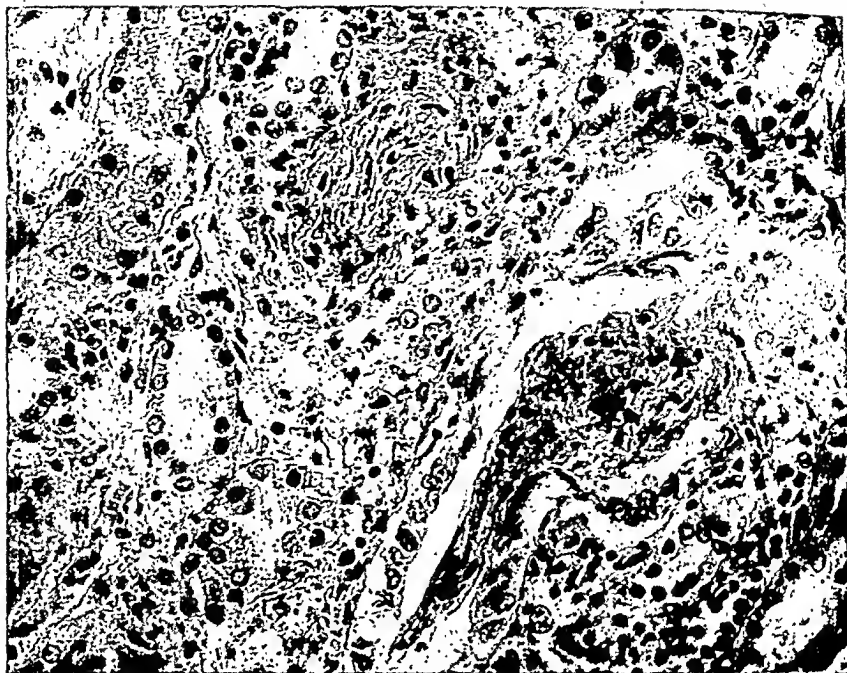


Abb. 7. Oben ein Konglomerat von hyalinen Schollen. Rechts unten ein teilweise zerstörtes Kanälchen mit ähnlichen hyalinen Massen im Lumen. Rundzelleninfiltrate in der Umgebung.



Abb. 8. Rundliche, streifige Eiweissniederschläge um ausgelaugte Kristalle im Nierenbecken.

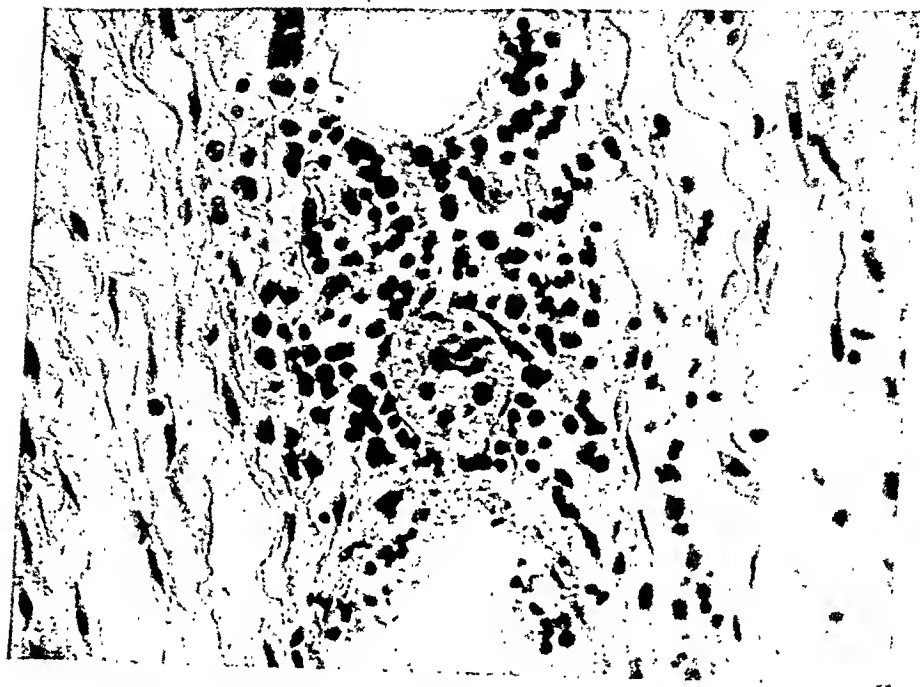


Abb. 9. Perivaskuläre Rundzelleninfiltration in der Nierenbeckenwand.

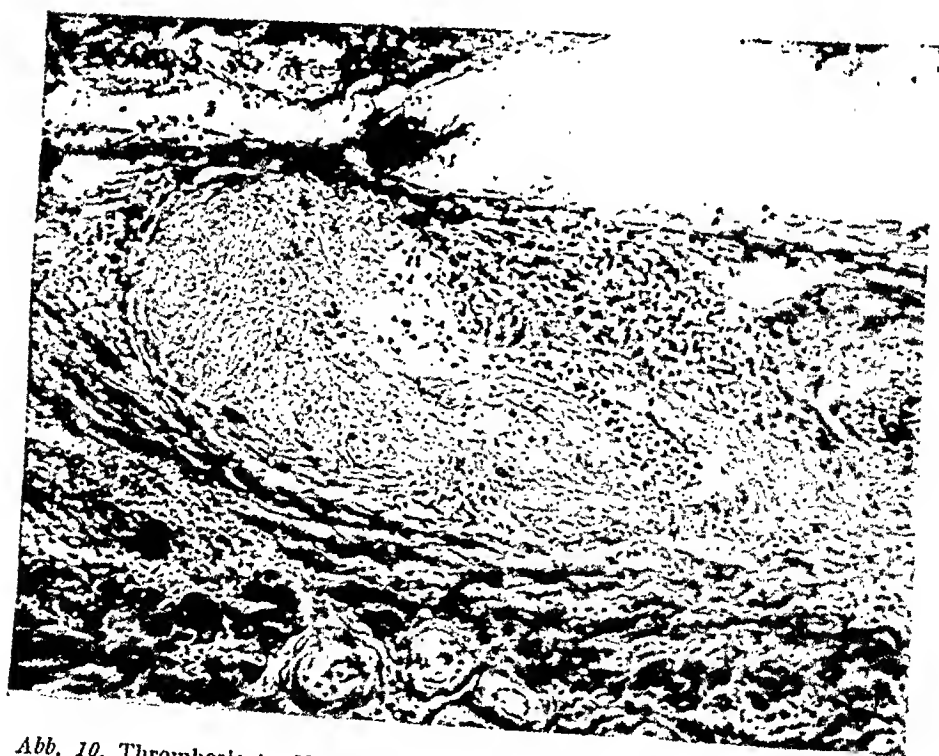


Abb. 10. Thrombosierte Vene mit perivaskulärer Leukozyteninfiltration in der Nierenbeckenwand an der Grenze des Hilusfettes.

Färbung aber blau. In einer Vene liegt ein Thrombus (Abb. 10) mit perivaskulärer Leukozyteninfiltration. Die Trombusmasse färbt sich ebenfalls bei *Mallory-Färbung* blau und gibt mithin nicht die Fibrinreaktion. Das Hilusfett weist kleine Nekrosen auf sowie ein Exsudat, welche bei *van-Giesonfärbung* den Eindruck von Fibrin macht, sich aber bei *Weigert-Färbung* nur teilweise und schwach positiv färbt und bei *Mallory-Färbung* blau wird.

Fall 4.

Obd. 344/43. ♂, 75 J. Wurde am 19. 11. wegen Hypernephroms der rechten Niere mit Perioden von Hämaturie aufgenommen. Rechte Niere am 30. 11. exstirpiert. Erhielt wegen Temperatursteigerung 21. 11.—23. 11. 16 g und 2. 12.—7. 12. 27 g Sulfathiazol. Am 3. 12. war die Sulfathiazolkonzentration im Blut 3,8 mg %. 6. 12.: Rest-N 56, Harnmenge klein. Der Reststickstoff stieg später bis über 100, und die Urinmenge sank weiter auf 200—300. Am 9. 12. wurde die linke Niere freigelegt und das Nierenbecken gespült. Das Becken war jedoch nicht ausgespannt. Gleichzeitig wurde die Dekapsulation vorgenommen, da die Niere geschwollen war. Sulfathiazolkristalle wurden nie im Urin gefunden. Exitus am 11. 12. an Urämie mit Krämpfen.

Pathologisch-anatomische Diagnose: Status post nephrectomiam.

Linke Niere wog 320 g. Nierenparenchym hyperämisch, schwellend. Im Nierenbecken sah man kleinere Blutungen, aber keine Konkreme. Die Harnleiter waren nicht erweitert und enthielten ebenfalls keine Konkreme. Dagegen fand man auch hier Schleimhautblutungen, desgleichen in der Blase.

Mikroskopische Untersuchung der Niere: Die Niere weist eine geringe Elastikahyperplasie in den Arterien auf, sonst aber keine arteriosklerotischen Veränderungen. Die Epithelien der gewundenen Kanälchen sind angeschwollen und granuliert, und in einem Teil der Kanälchen färben sich die Körnchen bei *Mallory-Färbung* rot. Es handelt sich hier also um eine leichte Degeneration in Form hyaliner Tröpfchen. Die Zellkerne sind nicht verändert. Die Ductuli papillares sind erheblich erweitert und mit Zylindern angefüllt. Im übrigen sieht man zerstreute Herde von hyperämischem Parenchym mit Blutungen in die Kanälchen. Ausserdem findet man zahlreiche kleine Partien, in welchen die Kanälchen zerstört sind, und wo das Gewebe an deren Stelle zahlreiche Rundzelleninfiltrate enthält. In einem Teil dieser Herde sind Reste von zugrunde gegangenen Kanälchen oder hyaline Bänder und Schollen sichtbar, welche in Klümpchen von etwa Glomerulusgrösse angesammelt liegen. Diese hyalinen Massen färben sich bei *Mallory-Färbung* blau, bei *van-Giesonfärbung* gelb. Die Glomeruli zeigen keine merkbaren Veränderungen. Nirgends sieht man Verfettung. Das Nierenbecken weist Schleimhautblutungen sowie Abschuppung der Epithelien auf. Im Hilusfettgewebe, aber nicht nur hier, sondern auch in der ganzen Fettkapsel, welche die Niere umgibt, bemerkt man eine reichliche Zellinfiltration, besonders von mononukleären Zellen, sowie ein fibri-

nöses Exsudat. Unter der Nierenkapsel ein grosser Bluterguss. Hämosiderinpigment im Ifilusfett in reichlicher Menge vorhanden.

Fall 5.

Obd. 273/43. ♀, 80 J. Erkrankte am 2. 10. 43 unter Stichen in der rechten Brustseite und Frösteln. Diagnose Bronchopneumonie. 8. 10. Exitus. Erhielt 2. 10.—7. 10. insgesamt 35 g Sulfathiazol sowie am 7. und 8. 10. zusammen 10,5 g Sulfathiazol. Zwölf Stunden vor dem Tode Krampfanfälle. In den letzten 24 Stunden Anurie, sonst aber keine Angaben über die Urinmenge.

Pathologisch-anatomische Diagnose: *Fibrosis myocardi + Bronchopneumoniae pulmon. ambor.*

Die Nieren wogen zusammen 210 g. In der Rinde sah man zahlreiche kleine Blutungen. Nierenbeckenschleimhaut blass. Keine Konkremeute.

Mikroskopische Untersuchung der Niere: Die Arteriae interlobulares weisen eine starke Elastikahyperplasie auf. Irgendwelche arteriolosklerotische Veränderungen sind dagegen nicht zu finden. Vereinzelte Glomeruli sind hyalinisiert, sonst sind die Nierenkörperchen intakt. Überall im Mark und der Rinde sieht man verstreute kleinere, hyperämische Stellen, teilweise mit Blutungen in die Kanälchen. Ferner bemerkt man zahlreiche Rundzellenherde, welche zerstörte Kanälchen umschliessen, oder Haufen von hyalinen Massen in Form von Bändern und Schollen. Die letzteren färben sich bei Mallory-Färbung blau. Die gewundenen Kanälchen zeigen keine Degeneration in Form hyaliner Tröpfchen, wohl aber eine feinkörnige Verfettung. Sammelröhrchen und Ductuli papillares nicht erweitert.

Fall 6.

Obd. 36/44. ♀, 55 J. Am 31. 10. 43 war der Patientin ein Hühnerknochen im Halse stecken geblieben. Sie wurde am 4. 11. aufgenommen, und da die Röntgenuntersuchung eine Perforation 4—5 cm unterhalb vom Speiseröhreneingang ergab, wurde der Ösophagus von der rechten Halsseite aus freigelegt. Trotzdem liessen sich Mediastinitis und Abscessbildungen am Hals nicht verhindern, und der Zustand der Kranken wurde immer schlechter, bis am 29. 1. 44 der Exitus erfolgte. S. auch Tab. 11. Während des Krankenhausaufenthalts erhielt die Patientin folgende Sulfathiazolmengen: 4. 11.—8. 11. 4,5 g, 12. 11.—20. 11. 8 g, 27. 11.—30. 11. 3,5 g, 5. 12.—7. 12. 2,5 g, 10. 12.—17. 12. 7 g, 20. 12.—25. 12. 5 g, 30. 12.—31. 12. 1,75 g, 3. 1.—4. 1. 1 g, 22. 1.—28. 1. 6,5 g.

Pathologisch-anatomische Diagnose: *Abscess. chronic. reg. coll. dextr. + Infarct. sept. pulmon. ambor. + Infarct. sept. mult. gangl. basal. cerebr. + Abscess. subcutan. cruris dextr.*

Die Nieren wogen zusammen 325 g. Parenchym hyperämisch. In der einen Niere fand man im Nierenbecken reichlich Sulfathiazolkristalle, und solche wurden in Form kaum sichtbarer Pünktchen auch im Parenchym festgestellt. Ureteren nicht ausgespannt.

Mikroskopische Untersuchung der Nieren: Die Nieren weisen in den Arteriae arciformes und interlobulares eine mässige Elastikahyperplasie

Datum	Urinmenge	Eiweiss	Reaktion	Rote Blutkörperchen	Weisse Blutkörperchen	Kristalle	Bact. coli
20. 11.	1750	Spur	sauer	+	+	+	0
30. 11.	1750	Spur	sauer		+	+	0
21. 12.	1000	Spur	sauer		+	+	+
19. 1.	300+	+	sauer			+	+
25. 1.	450						
26. 1.	300	+	sauer	+	+		+
27. 1.	750+						

Abb. 11. Obd. 36/44.

auf, aber keine arteriolosklerotischen Veränderungen. Die Epithelien der gewundenen Kanälchen sind angeschwollen, zeigen jedoch keine Verfettung oder Degeneration in Form hyaliner Tröpfchen. Im Lumen der Kanälchen schwach färbbare Körnchen und Fasern sowie vereinzelte hyaline Zylinder. Ductuli papillares ein wenig erweitert. Das Nierenparenchym ist überall hyperämisch. Ausserdem sieht man verstreute Herde mit Blutungen in die Kanälchen. Namentlich in Verbindung mit diesen Blutungen, aber auch an anderen Stellen, liegen kleinere Partien, in welchen die Kanälchen zerstört und durch Rundzelleninfiltration des Gewebes ersetzt sind. Im Zentrum dieser Partien bemerkt man glomerulus-grosse Klümpchen von hyalinen Schollen und Bändern, welche sich bei Färbung nach *Mallory* blau und bei derjenigen nach *Weigert* nicht wie Fibrin färben. Die Rundzellen geben nicht positive Plasmazellenfärbung. Im Nierenbecken sieht man Epithelabschuppung und Blutung. Das Fettgewebe am Hilus weist Rundzelleninfiltration und Blutung auf.

Fall 7.

Obd. 143/43. ♀, 57 J. Erkrankte Anfang März¹ 1943 an Husten und Stichen in der linken Seite. Aufnahme in das Krankenhaus am 22. 3. Erhielt eine Woche lang Sulfathiazolbehandlung mit ziemlich grossen Dosen. Bei Röntgenuntersuchung am 2. 4. wurde in der linken Lunge die Aufhellung einer zuvor festgestellten Verschattung konstatiert, zugleich aber lateralwärts eine stärkere Verschattung, offenbar auf Grund eines randständigen Exsudats. Bei der Probepunktion am 7. 4. wurde dünnflüssiger Eiter entleert. 10. 4. Thorakotomie, dann bekam die Kranke insgesamt 15 g Sulfathiazol während der Zeit 11. 4.—16. 4. Der Zustand besserte sich da wesentlich, Anfang Mai stellte sich aber wieder ein Fieber anstieg ein, und die Patientin erhielt da nochmals 15 g Sulfathiazol. S. Tab. 12. Am 10. 5. sank die Urinmenge bedrohlich, und es setzten urämische Erscheinungen ein. 13. 5. Exitus.

Datum	Sulfathiazol	Urinmenge	Urin- reaktion	Elweiss im Urin	Rote Blutkörperchen im Urin
8. 5.	5 g	1300			
9. 5.	5 g	1050			
10. 5.	5 g	100			
11. 5.		100			
12. 5.		200			
13. 5.			alk.	+	+

Abb. 12. Obd. 143/43.

Pathologisch-anatomische Diagnose: Empyema pleurae sin. operat. + Pneumonia chronic. pulmon. sin.

Die Nieren wogen zusammen 370 g. In der einen Niere eine grössere bindegewebige Narbe. Nierenparenchym hyperämisch. Auf der Schnittfläche sieht man an mehreren Stellen punktförmige, gelbweisse Flecken sowohl im Mark wie in der Rinde. Nierenbecken und Harnleiter nicht erweitert. Keine Konkreme in diesen. Leber vergrössert, von gelbroter Farbe.

Mikroskopische Untersuchung der Nieren: Die Kanälchen in der Rinde sind etwas erweitert, und die Epithelien derselben sind nicht so hoch wie normal. Die Lumina enthalten ein dünnes Netzwerk einer schwach färbbaren, geronnenen Masse. In den Epithelzellen sieht man keine Degeneration in Form hyaliner Tröpfchen, keine Verfettung und keine Veränderung der Kerne. Die Sammelröhrchen sind deutlich erweitert. Die Glomeruli sind im grossen ganzen intakt. In den Kapselräumen bemerkt man jedoch einen in geringer Menge vorkommenden Inhalt mit demselben Aussehen wie in den Kanälchen. Hier und da finden sich hyperämische Gebiete mit Blutungen in die Kanälchen. Namentlich im Anschluss an diese hyperämischen Partien werden Herde von Rundzellen beobachtet, in welchen die Kanälchen mehr oder weniger zerfallen sind. In einem Teil dieser Rundzellenherde stösst man auf Haufen von hyalinen Schollen und Bändern, die vereinzelte Epithelreste der Kanälchen umschliessen. Diese hyalinen Massen werden bei *Mallory-Färbung* blau und bei *van-Giesonfärbung* gelb. Derartige hyaline Schollen und Bänder kommen auch in einzelnen Sammelröhrchen im Lumen vor. In den Nierenbecken ist der Epithelüberzug zum grossen Teil abgestossen. Im Hilusfett sieht man grosse Rundzelleninfiltrate und auch kleinere Nekrosen. In Gefrierschnitten von mit Formalin fixiertem Gewebe wurden keine Kristalle gefunden.

Das makroskopische Bild der Nieren ist bei den vorstehend beschriebenen Fällen etwas wechselnd. Bei drei Fällen wurden

weder im Nierenbecken noch in den Harnleitern oder im Nierenparenchym Konkremeute gefunden. Derartige Konkremeute kamen dagegen bei den vier übrigen Fällen vor, und zwar teils im Nierenbecken und den Ureteren, teils im Parenchym. Im letzteren hatten sie die Gestalt kleiner, mit dem blossen Auge eben noch sichtbarer heller Pünktchen. Bei sämtlichen Fällen bestanden Hyperämien und Blutungen in das Parenchym, sowie gewöhnlich auch ins Nierenbecken. Ferner wurde im allgemeinen eine ödematöse Anschwellung der Nieren beobachtet.

Bei allen untersuchten Fällen sind die mikroskopischen Nierenveränderungen gleichartig und lassen sich folgendermassen zusammenfassen:

Die Glomeruli zeigen keine oder geringfügige Veränderungen in Form einer geringen Menge von geronnenem Eiweiss in den Kapselräumen. Die Kanälchenepithelien lassen eine gesteigerte Körnung erkennen, aber keine Verfettung oder Degeneration in Form hyaliner Tröpfchen und keine Kernveränderungen. In einzelnen Epithelzellen wurde jedoch einige Male eine geringgradige Degeneration in Form hyaliner Tröpfchen beobachtet. Die Lumina der gewundenen Kanälchen enthalten ein dünnes Netzwerk von geronnenem Eiweiss, welches sich bei *Mallory*-Färbung schwach blau und bei *van-Gieson*färbung schwach gelb färbt. Die Ductuli papillares sind bei einigen Fällen etwas erweitert. Die hervorstechendste Veränderung sind zerstreute herdförmige Rundzelleninfiltrate, welche im Zentrum einen Klumpen von hyalinen Schollen und Bändern enthalten. Ein derartiges Gebilde ist etwa so gross wie ein Glomerulus. Zwischen den Schollen liegen Rundzellen und vereinzelte Epithelzellen zerfallener Harnkanälchen. In gewissen Fällen befinden sich die Klümpchen im Innern eines ausgespannten Kanals, ein Hinweis darauf, dass sich die Schollen in den Kanälchen bilden. Diese hyalinen Gebilde färben sich bei *van-Gieson*färbung gelb, bei *Mallory*-Färbung blau und bei der *Weigert*schen Fibrinfärbung nicht wie Fibrin. Vereinzelte Schollen können allerdings eine schwache Fibrinfärbung geben. Das Nierenparenchym weist ausserdem Hyperämie und Blutungen auf, namentlich im Anschluss an die Rundzelleninfiltrate.

Im Nierenbecken werden Epithelablösung, Blutungen und Rundzelleninfiltrate in der Wandung beobachtet, sowie auch Thrombenbildung in den Venen. In oder auf der Schleimhaut kann

man radiär gestreifte, rundliche Körper antreffen, welche sich färberisch ebenso verhalten wie die obenerwähnten hyalinen Schollen und Bänder im Nierenparenchym.

Auch im Hilusfett finden sich bei allen Fällen Veränderungen in Form von Rundzellen- oder Leukozyteninfiltraten.

Die obengenannten radiär gestreiften Körper im Nierenbecken sind offenbar Eiweissniederschläge um Sulfathiazolkristalle, die bei der Präparierung des Schnitts ausgelaugt worden sind. Die Klümpchen hyaliner Schollen im Nierenparenchym sind allem Anschein nach analoge Gebilde, welche durch Ausfällung von Eiweiss auf Sulfathiazolkongrementen in den Nierenkanälchen entstanden sind. Diese Sulfathiazolkristalle haben den Zerfall der Kanalabschnitte, in denen sie liegen, verursacht, was Rundzelleninfiltration und Blutungen in die Umgebung zur Folge hatte.

Die Nierenschädigung ist mithin eine ausgeprägt herdförmige und an denjenigen Stellen lokalisiert, an welchen das Sulfathiazol ausgefallen ist. Im Nierenbecken lassen jedoch die Sulfathiazolniederschläge eine Fernwirkung in Form von Blutungen, Rundzellen- oder selbst einer Leukozyteninfiltration im Hilusfettgewebe erkennen. Auch Thrombosen können hier vorkommen.

Die Betrachtung der Krankenblätter lehrt, dass man nicht bei allen Fällen beweisen kann, der tödliche Ausgang sei eine Folge der Nierenschädigung. So fehlen bei Fall 5 Angaben über die Harnmenge und den Reststickstoff fast gänzlich, und Fall 1 ist so kompliziert, dass es unsicher ist, ob die Reststickstoffsteigerung auf der Nierenschädigung beruhte. Bei den übrigen Fällen dürfte allerdings Urämie unbestreitbar die Todesursache gewesen sein.

Es ist indessen durchaus nicht leicht, den Mechanismus beim Zustandekommen der Urämie im einzelnen festzustellen. Eine Glomerulusschädigung kann allen Umständen nach nicht in Betracht kommen. Ein mechanisches Hindernis für den Harnabfluss liegt bei einigen Fällen vor, aber nicht bei allen. Eine schwerere derartige Störung wurde nur bei einem Fall konstatiert. Hieraus ergibt sich offenbar, dass eine mechanische Behinderung dieser Art nicht die einzige Ursache der Urämie sein kann, wenn auch dieser Faktor in gewissen Fällen Bedeutung besitzen mag. Um eine diffuse Epithelschädigung schwereren Charakters handelt es sich ebenfalls nicht; dies steht in gutem Einklang mit dem Umstand, dass die im Urin ausgeschiedenen Eiweissmengen bei allen Kran-

ken äusserst gering waren. Die herdförmige Schädigung hat zwar zur Zerstörung etlicher Nephronen geführt, aber der hierdurch bedingte Funktionsausfall erscheint nicht gross genug, um die Urämie zu erklären. Bemerkenswert ist das regelmässige Vorkommen entzündlicher Zellinfiltrate im Hilusfettgewebe sowie die fast konstante Gewichtszunahme der Nieren. Man könnte daher in Erwägung ziehen, ob nicht vielleicht das entzündliche Ödem bei der Funktionsstörung die wesentlichste Rolle spielt.

Im Schrifttum wird über zahlreiche Fälle von Anurie berichtet, die nach Behandlung mit Sulfonamidpräparaten auftrat und durch Harnleiterkatheterismus oder operative Öffnung des Nierenbeckens mit Spülung behoben wurde. Ein derartiger Fall ist in Schweden schon 1941 von Sjövall und Lindgren beschrieben worden. Bei der Zystoskopie sah man, dass die Uretermündungen stark ödematös und geschwollen waren. Aus dem rechten Ostium ragte ein aus geronnenem Blut und Kristallen bestehender Pfropf hervor. Der Ureter liess sich nicht katheterisieren; man nahm deshalb die doppelseitige Pyelostomie und Dekapsulation vor, welche lebensrettend wirkte. Erst 8 Tage nach der Operation kam der Abfluss durch die Harnleiter wieder spontan in Gang. Bei diesem wie bei anderen Fällen lag offensichtlich ein entzündliches Ödem sowohl in der Niere wie in den Ureteren vor. Das Ödem der Harnleitermündungen hat im Verein mit Konkrementen und Blutgerinnseln im Lumen ein mechanisches Hindernis geschaffen. Zu diesem gesellte sich sicherlich die durch das Ödem in der Niere selbst bewirkte Funktionsstörung.

Leichtere Schädigungen dieser Art können ohne eine dauernde Störung der Nierenfunktion ausheilen; dies beweisen viele Fälle im Schrifttum, bei denen die Kranken nach Anfällen von Oligurie, Reststickstoffsteigerung sowie Blut und Sulfathiazolkristallen im Urin vollständig erscheinungsfrei wurden, nachdem man ihnen Flüssigkeit und Alkali zugeführt hatte. Es ist sogar möglich, dass Sulfathiazolschädigungen der Nieren vorkommen können, ohne klinische Symptome hervorzurufen. Ein von Loewenberg u.a. veröffentlichter Fall spricht hierfür.

Zusammenfassung.

Verf. beschreibt die pathologisch-anatomischen Veränderungen bei 7 Fällen von Sulfathiazolschädigung der Nieren, von welchen mindestens 5 an Urämie ad exitum gekommen waren. Die Veränderungen waren bei allen Fällen die gleichen und wurden von einer herdförmigen Zerstörung der Nierenkanälchen an denjenigen Stellen gekennzeichnet, an welchen Sulfathiazolkristalle ausgefallen waren. Rings um die Sulfathiazolkristalle in den zerfallenen Kanälchen wurden hyaline Eiweissniederschläge mit perifokaler Rundzelleninfiltration und Blutung konstatiert, welche dem mikroskopischen Bild ein äusserst charakteristisches Gepräge verliehen. Ausserdem wurden Epithelverluste im Nierenbecken und Blutungen in dasselbe beobachtet, sowie entzündliche Zellinfiltrate in seiner Wand und im Hilusfett. Verf. erörtert die Genese der Urämie und kommt zu dem Ergebnis, dass die wichtigste Ursache wahrscheinlich das durch ausgefallte Sulfathiazolkristalle in den Nieren und Harnwegen verursachte entzündliche Ödem ist.

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Inulin as a substitute for Creatinine in renal tests.

By

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The attention of kidney workers has during the last years increasingly gravitated towards the inulin method of Smith and his collaborators. At least in Sweden, however, there exists a certain want of clearness with respect to several points of interest in this connection, and this is not to be wondered at, seeing how difficult present general conditions render every kind of delicate and prolonged research, where intricate and long drawn out series of experiments are to be performed, and where an unwieldy mass of as a rule most conflicting literature is to be read and thoroughly digested.

Worst of all from the Swedish nephrologist's point of view, however, is the literary isolation consequent upon all neighbouring countries being occupied and practically all foreign intercourse broken since years. Library work is rendered very difficult, when current numbers of important foreign journals, and especially, more detailed papers are hardly procurable at all or only after long delay, and this is most inconvenient in a field like renal physiology, where the factors concerned are too numerous to be studied experimentally by one single worker or group of workers, and where, consequently, mutual interchange and discussion of experiences is imperative.

Prior to discussing the evidence alleged to confirm the conviction that the Inulin Clearance is at the level of glomerular filtration in the human kidney» (Homer Smith, *Physiol. of the kidney*, 1939 p. 26), we recollect that *the clearance of a urinary constituent* is defined as the volume of blood in cubic centimetres that is completely cleared of this substance during one

minute. In other words, Clearance equals the (minimal) blood volume required to contain the same amount of the substance as is contained in the urine formed during one minute.

As no natural urinary constituent is removed completely out of the renal blood, *the clearance blood volume is of course purely theoretical*. Only about 20 % of the creatinine of the renal blood is thus removed from this blood during its passage through the kidney, and the real volume of blood thus imperfectly cleared of its creatinine is therefore about 5 times the volume indicated by the clearance of the creatinine. All other natural urinary constituents have lower or very much lower clearances than creatinine and are removed from the renal blood only in fractions amounting to at most a few percent of their resp. totals in the blood of the kidney (cf. below page 145).

If we design clearance of a certain urinary constituent Cl , the blood and urinary concentrations of that substance C_b and C_u , and the volume of the urine U , the clearance of this substance is obviously

$$1) \quad Cl = \frac{U C_u}{C_b}$$

because if the substance in question were to be removed completely from a portion of the blood passing through the kidney during its excretion, the volume of blood to be thus cleared should amount to

$$\frac{U C_u}{C_b} \text{ cc.}$$

Moreover, if the substance in question passes in neither direction through the tubular walls during the tubular passage of the glomerular urine, i. e. if the tubules *neither* by secretion augment the glomerularly filtered amount of the substance *nor* subtract from that amount by resorbing more or less of the substance back into the blood, *then* it is obvious that the clearance of such a substance equals the volume of the glomerular filtrate. The glomerular filtrate, $F \text{ cm}^3$, must obviously contain neither more nor less of a substance, that is neither secreted nor resorbed by the tubules, than the urine formed out of that volume of glomerular filtrate. As the concentrations of filtrate constituents equal their concentrations in the blood, we may in this case write,

$$2) \quad F = \frac{U C_u}{C_b} = Cl$$

In the case of substances, however, that are *partially reabsorbed* back into the blood from the glomerular urine passing down the tubules, the filtered quantity is obviously larger than the amount recovered in the urine, that is

$$F C_b > U C_u \text{ or } F > \frac{U C_u}{C_b}$$

As $\frac{U C_u}{C_b}$ is the clearance value of any given substance, we can in such a case write

$$3) \quad F > Cl, \text{ or } Cl < F$$

The clearance of *tubularly resorbable substances* is thus no measure of the volume of the glomerular filtrate but gives a lower figure, and the more resorbable the substance is, i. e. the higher the resorbed fraction of the filtered quantity, the lower will clearance sink below filtrate volume.

Clearance and filtrate volume will obviously differ in the opposite sense, i. e. clearance will be higher than filtration, if the tubules add by secretion to the glomerular filtration of a substance. Here

$$U C_u > F C_b; \text{ that is, } \frac{U C_u}{C_b} > F$$

$$\text{As } \frac{U C_u}{C_b} = Cl, \text{ it follows that in this case}$$

$$4) \quad Cl > F$$

Smith and collaborators often use the expression *Concentration ratio* alternatively to Clearance. As the concentration ratio of a substance is the proportion between its concentrations in urine and the blood, $\frac{C_u}{C_b}$ it is obviously proportional to clearance.

As the Clearances of substances subjected to partial reabsorption in the tubules *necessarily are lower*, and those of substances, secreted by the tubules in addition to glomerular filtration, *necessarily are higher* than the Clearance of a substance *neither tubularly secreted nor resorbed*, the same holds true of their resp. concentration rates. If we design substances of the first and second groups with *r*, resp. *s*, and a substance neither secreted nor resorbed in the tubules with *o*, the clearances relate as

$$Cl_r < Cl_o < Cl_s \text{ or}$$

$$5) \quad \frac{U C_u r}{C_{b r}} < \frac{U C_u o}{C_{b o}} < \frac{U C_u s}{C_{b s}}$$

and the concentration rates relate as

$$6) \quad \frac{C_{u r}}{C_{b r}} < \frac{C_{u o}}{C_{b o}} < \frac{C_{u s}}{C_{b s}}$$

It is obviously important to decide, which, if any, among renally excretable substances is eliminated solely by glomerular filtration without any participating tubular secretion or resorption:

the clearance of that substance equals the *volume of the glomerular filtrate*.

Moreover, the *filtered amounts* of any filtrable urinary constituent equal the products of the filtrate volume and the plasma concentrations of the resp. substances; the *amounts* of these substances *resorbed* (or secreted) by the renal tubules are easily computed from their filtered quantities and their amounts in the bladder urine. Indeed, unless these data are known, it is hardly possible, except in very rare and special instances, to discuss any quantitative problems of renal excretion.

It is essential to bear the above simple formulas and deductions in mind, when we come to consider the question, whether inulin affords better means than creatinine of computing filtration volume. The evidence submitted in this question by Smith and his collaborators hinges in fact almost entirely upon the clearances of inulin, creatinine, and some other substances (chiefly more or less resorbable carbohydrates).

* * *

Comparisons between the inulin- & creatinine-clearances.

The principal fact, on which Smith and his collaborators build their arguments, is that inulin-clearance is lower than creatinine-clearance in man and some other species, especially the anthropoid apes.

The clearances of creatinine and inulin are said to average 175 resp. 125 cm³ in man, i. e. the *creatinine: inulin*-clearance rate should be 1.40 : 1 (Physiol. of the Kidney, p. 12 & 18). If the authors' tables (Tables 1, 2 & 3 from Smith & Clarke, Amer. J. Physiol. 1938, vol. 122, p. 134—36) are to be regarded as typical, the *creatinine-inulin*-clearance rate may be about the same in orang-utans as in man, is between 1.20 and 1.32 in gibbons and chimpanzes, is 1.14 a 1.17 in baboons, and varies between 0.98 and 1.20 in monkeys.

Creatinine and inulin clearances are said to be identical in frog, dog, rabbit, seal and sheep (Ibid., p. 132), and are indeed stated to »differ only in man and the apes, the chicken and the fishes»

(Homer W. Smith; *Kidney*, a literary review, *Ann. Rev. of Physiol.*, 1939, vol. 1. p. 503—28).

* * *

Turning now to the arguments to be derived from these differences of the inulin and creatinine clearances we remark in the first place, that the mere fact of a certain substance's renal clearance being of this or that order constitutes no independent proof as to whether this clearance equals, surpasses, or falls below the volume of the glomerular filtrate. This question can only be answered by comparing this clearance with the clearance of a glomerularly filtrable urinary constituent, the excretion of which can be definitely shown to be neither augmented nor lessened by tubular activity.

I regard it as superfluous to detail here the reasons earlier advanced in favour of the view, that creatinine is neither resorbed nor secreted by the tubules of healthy kidneys and that its clearance consequently gives the volume of the glomerular filtrate. It suffices to refer to my earlier monograph (G. Ekehorn, *Über die integrative Natur der normalen Harnbildung*, 1938), where the theoretical foundation and reliability of Rehberg's creatinine method is extensively discussed in chapter 4, where several important points to be observed in the execution of creatinine tests and in drawing inferences from their results are detailed in chapter 5, and where in chapter 13 numerous experiments are discussed, showing that the normal impassability of the tubular epithelium to creatinine has certain limits, and in badly diseased kidneys gives way to a more or less obvious inability to hold back all the filtered creatinine in the tubular urine, a phenomenon paralleled by increased permeability of the diseased epithelium towards urea. The creatinine method is therefore somewhat uncertain in the examination of badly diseased kidneys and remains a method for examining healthy or but slightly altered kidneys, where the results of adequately performed tests are highly reliable and possible to confirm in numerous and even rather unexpected details.

We can now pass over to the argumentation of Smith and collaborators which is simply this:

»The concentration ratio (cf. p. 116) of creatinine is very much higher than that of inulin in the dogfish, the red grouper, the chicken, and the anthropoid apes. This discrepancy is also evident in man; when creatinine is freshly injected into the blood it is concentrated by the human kidney about 40 % more than is inulin. Here either 40 per cent of (filtered) inulin is reabsorbed (in the

tubules) or considerable creatinine is excreted by the tubules in addition to that which is filtered» (Homer W. Smith, *Physiol. of the kidney*, p. 12).

That is to say, Smith states quite correctly *that* inulin must be subjected to partial reabsorption in the tubules, if creatinine is considered according to Rehberg to be neither secreted nor reabsorbed by the tubules, *resp. that* the tubules must secrete part of the urinary creatinine, if one regards inulin with Smith as being neither secreted nor reabsorbed by the tubules. The resorbed *resp.* secreted fractions of inulin and creatinine must in either case obviously correspond to the difference in the clearances or concentration rates.

Although the question is stated to be «important, since on the basis of Rehberg's early investigations, the creatinine clearance is widely accepted as a measure of the rate of filtration», the crucial problem of deciding which of the two substances is excreted without reabsorptive or secretory tubular participation, is nevertheless tackled in the following somewhat surprising manner:

«How can one exclude the possibility of some, even if slight, tubular reabsorption of inulin, which is a carbohydrate¹ even if a large and very inert one? This question was answered in the dog by Shannon, who showed that creatinine and inulin were concentrated to precisely the same degree» (and consequently had exactly similar clearances). «Similar identity in the concentration ratios (and clearances) has been demonstrated in the rabbit, the seal, the sheep, and, as Forster has recently shown, in the frog. Since it is implausible that two substances of such different natures as inulin and creatinine should be either excreted or reabsorbed by the tubules to precisely the same extent in these different species of animals, it may be accepted that *in these species both substances are excreted by filtration without tubular participation*,» (ibid. p. 11—12).

I agree entirely with the last conclusion, but object to the idea of deriving in this manner any argument for «excluding the possi-

¹ Carbohydrates are as a rule easily demonstrable by several independent methods to be reabsorbed by the tubules out of the glomerular filtrate. Glucose is normally resorbed completely already in the proximal parts of the tubules, the reabsorption of more complex or bodyforeign carbohydrates being less extensive, cf. below pp. 124—25.

bility of some, even slight tubular resorption of inulin in other species where inulin clearance falls below that of creatinine.

When for man, anthropoid apes, chicken and some fishes the question is to be decided, as to *whether* the renal tubules resorb inulin while not secreting creatinine or *whether* they reabsorb no inulin out of the filtrate while excreting some creatinine into it, no significance can be attached to *the finding, that in other species neither substance appears to be secreted nor reabsorbed by the tubules.*

In man and other species with higher creatinine than inulin clearance the choice is between either of these two alternatives;

a) *secretion of part of the urinary creatinine and no reabsorption of inulin in the renal tubules;*

b) *no tubular secretion of creatinine but tubular reabsorption of part of the glomerularly filtered inulin.*

No argument for or against the one or the other of these alternatives can possibly be derived from the finding, that the two clearances are identical in certain species, and that the tubules here consequently do not excrete or reabsorb any inulin or creatinine. The question, whether creatinine-clearance is larger or whether inulin-clearance is less than the real filtrate-volume in man etc., cannot possibly be decided by any reference to other species, where both clearances equal the filtrate-volume.

Smith commits a very grave logical error when attempting to support the alternative a) and to rule out alternative b) with findings that conflict with both alternatives. In doing so, he constructs an argumentative sequence of an altogether illusory nature, as he takes account only of a certain part of the findings from frog, dog, rabbit, seal, and sheep, namely, that no filtered inulin is resorbed by the renal tubules of these species. He disregards entirely the remaining half of the same findings, namely that the tubules of these animals do not secrete any creatinine, and he forgets that *this part* of the findings conflicts with the first implication of alternative a) quite as much as the other part of the same finding conforms to the second implication of alternative a).

The altogether illusory nature of such reasoning becomes obvious, if we repeat Smith's argumentation with the difference, that we discard from consideration that part of these findings on frogs, dog etc. that refers to inulin and take account only of what refers to creatinine. We should then say, that alternative a), (i. e.

tubular secretion of creatinine) is out of the question in man and apes, as tubular secretion of creatinine does not occur in frog, dog etc.; hence, only alternative b) had to be considered, and the difference between the inulin- and creatinine-clearances in man and apes should be due to tubular resorption of filtered inulin!

In other words, in man and apes the clearances of inulin and creatinine relate to each other in the manner of the equation

$$x : y = a$$

where $a \leq 1$, but they relate to each other according to the equation

$$x : y = 1$$

in frogs, dog, rabbit, seal, sheep etc.

These equations, however, contradict each other and cannot possibly be combined and introduced into a common equational system.

* * *

It is therefore the more surprising to find Smith end up the above line of argumentation with the remark (Smith, *Physiol. of the Kidney* p. 12), that he feels the evidence, criticized here, «conclusive», although he admits it not having been able «to convince all investigators». «It is gratifying», continues Smith, «that we are able to add supplementary facts at this time».

Still more surprising, however, is the circumstance, that the evidence detailed on the following page 13 of Smith's book has no bearing whatever on the two questions to be decided, *namely whether* inulin is not reabsorbed and creatinine consequently is partly excreted by the renal tubules of man, antropoid apes, chickens and fishes, *resp. whether* creatinine is not excreted and inulin consequently is partly reabsorbed in the renal tubules of the said species.

The numerous investigations quoted here by Smith show in fact a) that inulin is filtrable in the glomeruli of frog and *Necturus*, b) that inulin and creatinine have equal clearances in the dog, and c) that neither creatinine nor inulin is excreted by the tubules of frog, rabbit, and dog. Although these findings are interesting in themselves, *none of them contains any observation bearing on pos-*

sible tubular reabsorption of filtered inulin in the kidneys of the Anthropoids or man, and still less any observation negating such reabsorption. *None of these observations contains further any evidence in favour of tubular excretion of creatinine.* Those observations contain in fact no »supplementary evidence» whatever in favour of Smith's view of tubular creatinine excretion and tubular non-reabsorption of inulin in man, apes etc.

As a matter of fact, the evidence of Smith's point b) is not supplementary to his main argument, as identity of the inulin- and creatinine-clearances in the dog is a fact already comprised in the main argument and found to afford no means of deciding the issue discussed. Nor have his points a) and c), i. e. that inulin is excreted by glomerular filtration and not by tubular secretion, any bearing on the question, whether or not filtered inulin partly is resorbed in the tubules of man and apes. It must be recollected, that the renal tubules of man according to Smith's own express statement reabsorb about 50 % of filtered urea and on an average reabsorb no less than 124/125 of the filtered water. Excretion by means of glomerular filtration is, of course, no guarantee against subsequent tubular resorption of even very large fractions of the filtered amounts.

* * *

Nevertheless Smith continues on pp. 13—15 of his book:

»Deferring for a moment further discussion of the excretion of inulin in man, we will tentatively assume that this polysaccharide is filtrable through the glomeruli in the same concentration per unit of water as it is present in the plasma; thereafter it passes down the tubules like a stream of inert marbles, the filtered quantity suffering neither increase nor decrease in consequence of tubular excretion or tubular reabsorption». Some simple consequences of this conception are then sketched and illustrated by rather obvious diagrams, whereupon the above »tentative assumption» is restated in the following very positive manner, no further evidence having been submitted so far: »Rewording the above discussion, we may say that inulin is cleared from the plasma exclusively by a process of glomerular filtration, unmodified by tubular reabsorption or tubular excretion».

This passage from a »tentative assumption» to a most posi-

tively worded assertion is most startling, *as no evidence* has been submitted between mere assumption and positive assertion, *and as the evidence* submitted prior to the tentative assertions is of an altogether illusory nature.

* * *

The clearances of several sugars compared with the clearances of inulin and creatinine.

Very surprising are also those inferences from the renal behaviour of carbohydrates, which Smith submits in support of his view of creatinine being excreted and of inulin not being reabsorbed by the renal tubules of man, anthropoid apes, chicken, etc. Prior to discussing those inferences, however, we must recapitulate several points concerning the renal fate of various carbohydrates. Some detail is required here, as it is exceedingly difficult even for the initiated reader to follow Smith and his co-workers' discussion. Their argumentation is open to many remarks, as many relevant observations bearing on the question inulin versus creatinine often are found in other places in their papers. Also the more comprehensive discussions of this question are often repeatedly interrupted by lengthy escapes into quite other matters or by masses of literary quotations with no bearing on the main theme (cf. p. 122 above). Nor is the argument, when proceeded with again after such digressions, always taken up where it was left. Most embarrassing to the reader, however, is the repeated occurrence of incomplete consideration of experiences bearing on the main question. Thus, for instance, only a certain part of the experimental evidence may be taken into consideration, although the remainder of the same evidence has as much bearing on the same question and, indeed, may profoundly affect the inferences drawn. This is very confusing, especially as Smith's argumentation proceeds on so enthusiastic lines that the reader easily forgets or fails to notice the omitted parts of the observations discussed.

* * *

Tubular resorption has been demonstrated in the case of glucose and a great number of other carbohydrates.

As to *glucose*, the facts of its regular presence in the blood and its absence from normal urine are already certain proofs of its tubular resorption, as it is established beyond doubt that glomerular urine is an ultrafiltrate from plasma containing all filtrable plasma constituents in their plasmatic concentrations (cf. Ekehorn, Principles of Renal function p. 348—472—476. Ekehorn »Über die integrative Natur der normalen Harnbildung p. 30—31, 89—109. Ekehorn, Virchow's Archiv, vol. 285, p. 455—60.) This is also confirmed by puncture experiments on amphibian kidneys, as chemical examination of withdrawn glomerular fluid shows glucose always to be present, as long as there is glucose in the blood (hibernating frogs may have glucose-free blood sometimes); attempts to estimate the glucose quantitatively in glomerular urine show concentrations so near its plasma concentration as to come within the analytical error of such exceedingly difficult and rather uncertain determinations. Tubular resorption of all the filtered glucose (unless there is hyperglucosaemia) is evident in frogs from the absence of glucose from simultaneously formed bladder urine, and is confirmed by tubular punctures showing it to disappear from the urine already in the proximal part of the first convoluted portion of the tubules in frogs (cf. Ekehorn, Über die integr. Natur der normalen Harnbildung, p. 1407, Glucose, and 1420, Punktionsversuche.). First in hyperglycaemia, when abnormally much glucose is filtered in the glomeruli, do more or less considerable fractions of filtered glucose escape tubular resorption and appear in the bladder urine.

Fructose has not been much used in renal experiments, but its close chemical affinity to glucose, its occasional occurrence together with glucose in diabetic urine, its rare occurrence in non-diabetic urines in spite of its not unfrequent, and according to some authors regular presence in small quantities in the blood, and in trans- and exudates, and several other circumstances as for instance the high degree in which it is utilized by the body — everything points decidedly in the direction that fructose and glucose behave rather much in the same way in the kidney. Thus fructose is about as readily filtrable in the glomeruli and as resorbable in the tubuli as glucose, and in no way are we justified in regarding fructose as badly resorbable in the tubules.

I have suggested, that the high tubular resorbability of these sugars depends on the fact of their having a common isomer, *enol*, which is a pretty strong acid, readily dissociates electrolytically, and always appears in minute, stoichiometrical proportions in glucose- and fructose solutions. This would bring the very complete reabsorption of these sugars in line with the resorption of electrolytes going on in the proximal portion of the tubules (Ekehorn, Über die integrat. Natur d. norm. Harnbild., p. 1037—40). We must recollect, that only a minute fraction of the glomerularly filtered electrolytes makes its escape into the bladder urine as is well illustrated by the curves 6 and 7, p. 174—75 of the quoted book.

The fact is that other sugars, used in renal experiments, none of which have enol as an isomer, are very much less resorbable in the tubules than glucose and fructose.

Lactose, when escaping in traces into the blood from the mammar glands

during lactation and the last periods of pregnancy, appears readily in the urine, and its clearance, though lower than the clearances of both inulin and creatinine, yet comes sufficiently near the latter to make it possible to use lactose as a means of approximately estimating the volume of the glomerular filtrate (Ekehorn, *Über die integr. Natur d. normalen Harnbildung*, p. 493—501—503).

Xylose is another badly resorbable sugar, that has been used a good deal in renal research as have also *Sacharose* and *Raffinose*. Indeed, these three sugars were at first believed not to be resorbable at all in the renal tubules or not reabsorbable to any appreciable degree, and were believed to have very much the same clearances and concentration ratios as creatinine, the complete tubular irresorbability of which has never been disputed for healthy renal tissue.

This opinion, which also the present author to some degree has shared, was based chiefly on the earlier works by Smith and his co-workers; their later investigations, however, have shown that xylose and sucrose are to some extent reabsorbable in the renal tubules (Smith, *Physiol. of the Kidney*, p. 10—11) (*Raffinose* appears not to have been reexamined).

The clearances and conc. ratios of xylose and sucrose are said by Smith to amount to c:a 80 % of clearance and conc. rates of inulin in dog, sheep, man, and certain fishes. As inulin-clearance equals creatinine clearance in dog and sheep, but only amounts to some 70 % of the latter in man, the clearances of xylose and sucrose may be 80 % of the *creatinine* clearance in dog and sheep and only 56 % of the *creatinine* clearance in man. That is to say, about 20 % of filtered xylose and sucrose should be reabsorbed by the tubules of dog and sheep; in man 20 % should be thus reabsorbed if inulin clearance is the correct measure of glomerular filtration, and slightly over 40 % if creatinine clearance is the correct measure.

* * *

The idea of partial tubular reabsorption of xylose etc. does not rest, however, merely on the fact that its clearance and concentration ratios are lower than those of inulin and creatinine (cf. the formulas p. 115 & 116). This idea is definitely confirmed also by the result of experiments where the tubular mechanism for glucose reabsorption is so to say saturated by a strong elevation of plasma glucose. I append a table from Shannon (James A. Shannon, *Tubular reabsorption of xylose in the normal dog*. *Amer. J. Physiol.*, 1938, vol. 122, p. 778).

We see from the table, that xylose clearance, which at first during normoglycaemia amounts to 78—81 % of creatinine clearance, rises to equality with the latter during the experimental periods 4—6 and 10—12 when glucose in plasma has reached the

Table 1.

Showing the effect on reabsorption of the saturation of the glucose reabsorption mechanism by an elevated plasma glucose

Experiment 36D, November 5, 1937. Dog G, weight 20 kgm., S. A., 0.81 sq.m. The clearance ratios starred are periods showing frank glycaemia.

Period	Time	Urine flow	Plasma concentration			Clearance		Clearance ratio
			Glucose	Creatinine	Xylose	Creatinine	Xylose	Xylose Creatinine
		cm ³ per min.	mgm per cent	mgm per cent	mgm per cent	cm ³ per min.	cm ³ per min.	
	0 10 15	500 cm ³ water by stomach tube 3 grams creatinine and 5 grams xylose intravenously Infusion 6 cm ³ per minute: creatinine 0.7 per cent, xylose 1.5 per cent						
1	:31- :40	10.22	67	31.3	84.7	74.3	58.0	0.781
2	- :51	9.63		32.2	82.6	70.1	57.2	0.815
3	-1:01	9.90	72	33.0	81.0	71.6	56.7	0.792
	1:02	Infusion 6 cm ³ per minute: creatinine 0.7 per cent, xylose 1.5 per cent, glucose 20 per cent						
4	1:30-1:40	11.20	403	34.0	74.3	76.8	79.8	1.040*
5	-1:49	10.85		33.7	74.1	77.3	77.6	1.004*
6	-1:59	10.60	467	33.8	75.2	79.0	77.6	0.982*
	2:02	Infusion 6 cm ³ per minute: creatinine 0.7 per cent, xylose 1.5 per cent, glucose 4 per cent						
7	2:25-2:36	5.82	304	34.7	82.6	69.3	64.9	0.937*
8	-2:45	5.30		35.1	83.7	73.1	66.9	0.915
9	-2:54	5.00	260	35.4	84.2	74.2	67.2	0.905
	2:57	Infusion 6 cm ³ per minute: creatinine 0.7 per cent, xylose 1.5 per cent, glucose 40 per cent						
10	3:19-3:28	14.00	807	33.2	78.3	79.3	81.8	1.132*
11	-3:48	14.20		32.8	77.1	76.9	76.4	0.993*
12	-3:55	17.15	921	32.6	75.6	80.1	80.9	1.010*

very high figures of 403—467 mg per cent, resp. the still higher figures of 807—921 mg per cent. There is marked glycosuria and polyuria during the whole of these periods. The effect is somewhat less marked during periods 7—9, where plasma glucose varies between the figures of 260—304 mg per cent and where glycosuria and polyuria are less; yet xylose clearance is already here distinctively elevated over the «normal» and amounts to 90—94 % of creatinine clearance. It is worth attention that the xylose concentration in plasma remains very much the same during the whole of this experiment, and that the small concentration variations that occur bear no relation to the differences of xylose clearance.

The following conclusions can be based on these results:

a) As long as the reabsorptive mechanism of the tubules for glucose — the existence of which is rendered beyond dispute by the evidence referred to on p. 124 above — has to resorb just the ordinary amount of filtered glucose it has still resorptive powers to spare, especially when blood sugar concentration is decidedly below the threshold as in periods 1—3. Not being engaged to its full capacity in reabsorbing the glucose, this mechanism reabsorbs in addition a fraction of the filtered xylose.

b) The chances of the glucose-resorbing mechanism having capacity to spare for reabsorption of the rather badly resorbable xylose are progressively lessened in hyperglycaemia, when so much glucose is contained in the filtrate, that this mechanism fails to reabsorb all the glucose from the glomerular filtrate streaming down the tubules. Although lessened, these chances are not quite abolished, however, so long as the glycosuria is moderate as in periods 7—9.

c) With massive hyperaemia and marked glycosuria, i. e. when an abundance of glucose-molecules are left back in the tubular urine, the competition of these molecules prevents the inert xylose molecules from reaching the reabsorptive tubular mechanism, so that the latter have practically no chance to get caught and reabsorbed, and the whole or very nearly the whole of the filtered xylose passes down into the bladder urine.

No objection can possibly be raised against Shannon and Smith's interpretation of these experiments in so far as it conforms to the arguments raised sub a) to c): xylose is affected by the

normal tubular reabsorption of glucose, so that a fraction of the filtered xylose is as it were sucked up by the tubules conjointly with the glucose; during hyperglycaemia the tubular mechanism for reabsorption of glucose becomes »saturated» with glucose, fails to reabsorb as much xylose as before, and finally the xylose is shut out completely from reabsorption by the excess of glucose. The clearance of xylose will thus approach and finally become identical with creatinine clearance, neither substance being reabsorbed by the tubules.

The ideas, that xylose is partly reabsorbed in the tubules, and that it is reabsorbed by the tubular mechanism resorbing glucose, are made still more evident by experiments with phloridzin. Increasing doses of phloridzin given for instance to a dog will, in fact, gradually change xylose clearance from a value well below creatinine clearance to equality with the latter, and this effect is incontestably due to phloridzin blocking glucose reabsorption in the tubules (cf. below p. 137). Blocking that mechanism so that it is rendered quite inactive and unable to reabsorb any glucose at all, is of course another way of preventing xylose being resorbed by it.

Before passing over to other experiments, however, emphasis should be given to the fact, that the behaviour of xylose in hyperglycaemia according to Shannon's paper reveals nothing whatever enabling us to decide the question, whether inulin or creatinine clearance is the correct measure of filtrate-volume in such species where the two clearances differ. It will be remembered, that dogs, the objects of Shannon's experiments, are among those animals, where creatinine and inulin have equal clearances and concentration rates; when xylose with increasing degrees of hyperglycaemia reaches a clearance and a concentration rate equal to those of creatinine, these therefore obviously equal those of inulin as well. All we can say is, that cessation of tubular xylose reabsorption rendering xylose clearance identical with creatinine *and* inulin clearances is another strong argument against tubular excretion or resorption of *either* creatinine or inulin as far as dogs and other species with identical creatinine and inulin clearances are concerned.

It is therefore rather curious to find Shannon's results referred to in the following way by Smith (Smith, *Physiol. of the kidney*, p. 24). »Shannon has recently shown» (in the paper, quoted above) »that in the dog and man (unpublished) during hyperglycae-

mia, when the glucose reabsorptive mechanism is loaded to capacity, xylose is excluded from tubular reabsorption, and the xylose clearance rises to identity with the inulin clearance.

Although the statement is correct in that sense, that a quantity which equals creatinine clearance in dogs also equals inulin clearance, it is nevertheless a curious form of reference to a paper, where xylose clearance in fact has been compared only to creatinine clearance, and where inulin is not mentioned with one word. Nor is Smith's statement happily formulated in view of the impression that it is likely to produce on readers without very special knowledge in these matters or who we unprepared to employ much time and criticism in finding out the facts behind the words. Smith's omission of every reference to creatinine is no doubt likely to create in such readers the impression of a strong point having been scored in favour of inulin in the question inulin versus creatinine. It is a *conditio sine qua non* for a substance to be used for determination of the filtrate volume that the tubules do not augment or diminish its filtered amount. If it can be indirectly derived from Shannon's experiments, that this is true of inulin in dogs why not mention that it is equally true of the substance actually examined, creatinine, and why not point out, that the experiment advances no argument in favour of the one more than of the other substance.

Equally obscure is Smith's reference to Shannon's at that time unpublished paper on xylose during hyperglycaemia in man. (It has been inaccessible in Sweden at present) I cannot but regret Smith's omission to give any particulars of that experiment. It is true, that the clearances of inulin and creatinine differ in man, but nothing whatever can be regarded as having been established in the question, as to whether inulin is a truer measure of filtration than creatinine in man, as long as we are not informed of whether, for instance, the clearances of xylose and inulin during hyperglycaemia have at all been compared with that of creatinine. Does, in other words, the inulin clearance still remain lower than creatinine clearance, or does it approach to or even become identical with the latter during hyperglycaemia in man, as is the case with xylose clearance in dogs? Finally, what degree of hyperaemia was induced in the test persons? It must be remembered, that a blood sugar level of over 400 mg per cent is required in dogs (cf. table, 1) in order to render the clearances of xylose and creatinine equal, although they ordinarily differ by no more than as 75—80 to 100, meaning, that only 20—25 % of filtered xylose is reabsorbed. In man there may be a question of excluding *two foreign carbohydrates* from partaking in glucose reabsorption, the one of which is resorbed

to about the same degree as is xylose in normal dogs, and the other one to about twice that degree (about 20 per cent of filtered inulin and about 44 % of filtered xylose may be resorbed in man (cf. figures p. 125). Conceivably a degree of hyperglycaemia very much higher than 400 mg per cent may be required in man before this occurs. Is such a degree of hyperglycaemia possible to induce experimentally in man without the gravest inconvenience to the experimental subject? Again, if it has not been reached, Shannon's unpublished experiments can hardly be regarded as conclusive.

* * *

Phloridzin experiments.

Turning now to the behaviour of *carbohydrates in phloridzinised kidneys* the matter is summed up by Smith in this surprising way (Smith, *Physiol. of the kidney*, p. 25). »It has long been known that the drug phloridzin induces glucosuria at all plasma levels, and in our first studies we attributed this to the blocking of the reabsorption of glucose in the tubules», (reference is here made to a paper published 1932 by Joliffe, Shannon, and Smith). »When phloridzin is administered to dog or man the process of sugar reabsorption by the tubules is completely abolished so that not only the glucose but also the xylose and sucrose clearances are nearly or quite identical with the inulin clearance, and prior to direct examination, we may anticipate that after phloridzin this identity will include sorbitol and mannitol.» (Sorbitol and mannitol are two hexahydric alcohols, the clearances of which are said practically to equal inulin clearance in dog and man, (cf. Smith, *ibid.* p. 23—24.)

Although both these sentences are perfectly correct on strict literal interpretation, yet they do not cover the whole of the matter and do not assist the reader to orientate himself objectively and adequately.

* * *

Turning to the first of the two quoted sentences, it is certainly not wrong in a strictly formal sense to say that phloridzin has long been known to induce glucosuria irrespectively of the level of the plasma glucose and to say that Smith and his collaborators »in their first studies» published 1932 interpreted this phenomenon as due to blocking of tubular glucose reabsorption. Nevertheless, a reference at least to Leif Poulsson had not been

out of place in a book like Smith's «Studies in the physiology of the kidney», the chapters of which were originally delivered as honorary lectures at a distinguished university, especially as Poulsson's clever work forms the basis of so many of Smith's and his collaborators' own studies. De Boer and Verney were the first to perform this experiment and to elucidate the mechanism of phloridzin diabetes (J. Physiol. vol. 58, 1923, p. 433) Poulsson reinvestigated the matter and succeeded in making observations of wide interest to renal physiology in general (ibid. vol. 69, 1930, p. 411). Poulsson confirmed that phloridzin diabetes is due to the drug blocking the normal tubular reabsorption of glucose. This was incontestable already because of the observations contained in his own paper, and it has never been seriously disputed afterwards. On the contrary, it appears now still more definite in view of later advance and experience of renal physiology. Nor is the other major result of Poulsson's paper without interest in this connection, as it forms the starting point and the basis of all such experiments, including those of Smith and collaborators, where concentration ratios and clearances of various substances are equalized to those of substances, held to be normally unaffected by tubular activity and therefore suitable for determining the volume of glomerular filtrate. Finding that in the sufficiently phloridzinised dog the concentration ratio of the glucose regularly rose from zero before phloridzination to over 75 à 90, in other experiments even to over 95 % and 98 % of the concentration ratio of creatinine, Poulsson found in this a strong support of the renal filtration reabsorption theory as well as of the reliability of Rehberg's method; this was so much the more the case, as Poulsson was able to refer to similar results with inorganic sulphate injected into the blood of unphloridzinised dogs. Seeing that two so different stuffs as creatinine and inorganic sulphate are concentrated by the kidney to almost the same very high degree (and consequently have almost equal, high clearances), and seeing that glucose is brought quite into line with these two under conditions only to be understood as blocking of its normal and undisputable tubular reabsorption, we cannot wonder at Poulsson's statement as to the improbability of any process of renal secretion partaking in the excretion of any of these three substances. It is but natural that Rehberg with great interest accepted this support for his creatinine method. At the same time Rehberg's critical acumen is underlined by the fact that he clearly realized, that comparisons between clearances and concentration ratios offer no incontestable means of verifying neither the filtration reabsorption theory as such, nor tests like his own method. With this critical standpoint also I entirely agree (Ekehorn, Principles of renal function, p. 677—79 and Über d. integr. Natur d. normal. Harnbildung, p. 101—05).

Turning now to the second of the two sentences quoted above on page 130 we do not for a moment dispute the formal correctness of the statement, that phloridzin renders the clearances and concentration ratios of not only glucose but also of xylose and sucrose, and presumably also of sorbitol and mannitol, equal with inulin clearance and concentration ratio.

Apparently, the quoted statement gives the impression of a good many important points having been scored in favour of the inulin method. Inulin appears as a substance, or rather as the substance which is unaffected by tubular reabsorptive activity, when quite a number of substances like glucose and xylose — that otherwise are reabsorbed completely or partially out of the glomerular filtrate streaming down the tubules — have the same clearance and concentration rate as inulin only when tubular reabsorption of glucose and other carbohydrates is paralyzed by phloridzin. If the reader then recollects the evidence detailed by Smith on p. 13 of his book (cf. p. 121 above) showing that inulin is filtrable in the glomeruli and that it is not secreted by the tubules, an extraordinary degree of critical acumen will certainly be required in him for not to infer, that inulin, being filtered in the glomeruli and apparently neither secreted nor reabsorbed by the tubules perfectly satisfies all requirements for a substance to be used (p. 115) for computing the volume of the glomerular filtrate, this in contradistinction to creatinine on the suitability of which Smith casts so many doubts. Such inferences simply cannot be avoided, when the quoted statement as in Smith's book comes on the top of repeated assertions that this is the correct way in which to regard these matters.

The total irrelevance and inadequacy of such inferences becomes obvious, however, on taking the following point into consideration. The clearances and concentration rates of glucose, sucrose, xylose etc. during phloridzination equal clearance and concentration rate of creatinine quite as much as those of inulin, because according to the investigations by Smith and his collaborators themselves the clearances and concentration rates of inulin and creatinine are:

Either identical with one another at the outset (frog, dog, seal sheep, rabbit etc.), and they remain identical under phloridzin.

Or they will get equal with one another under phloridzin in

those species where they differ in the not phloridzinised kidney (man, antropoid apes, etc.) (cf. table 2).

The argument apparently contained in the fact, that xylose, suerose, glucose etc. obtain identical or almost identical clearances with inulin under phloridzin contains therefore nothing whatever enabling us to preclude the following possibilities: 1) that inulin is subjected to partial reabsorption by the tubules of such species where inulin has a lower clearance than creatinine; 2) that this resorption of inulin ceases and its clearance is rendered equal with that of creatinine during phloridzination; 3) that in such species inulin behaves just as xylose and suerose always do when tubular earbohydrate reabsorption is specifically paralyzed (phloridzin) or otherwise blocked to foreign carbohydrates.

The only differences between inulin and other carbohydrates would then be, *that* xylose and sucrose are partially reabsorbed in the tubules of *all* species, whereas inulin is only so reabsorbed by some species (man, apes, chicken), *and that* phloridzination therefore will affect the clearances of xylose, sucrose, and glucose in all species, rendering them equal with creatinine clearance, whereas it can affect inulin clearance only in those species where inulin clearance prior to phloridzination differs from creatinine clearance. Inulin clearance cannot, of course, be affected at all in those species (dog, rabbit, seal, sheep etc.) where inulin is never resorbed and where cessation of sugar reabsorption thus causes no increased fraction of the filtered inulin to pass down into the urine.

* . *

Deferring for a moment further remarks on this subject, we submit here a table from Smith and Clarke (Smith and Clarke Amer. J. Physiol., 1938, vol. 122, p. 132-39) showing *the equalisation of inulin and creatinine clearances during phloridzination* of a chimpanzee. Although only the lower half of the table details the effect of phloridzin, we reprint also its upper portion, that will be referred to below. The very significant data of our column VIII are omitted in Smith and Clarke's original table; they are easily computed, however, from their data in columns VII and IX.

Looking at the data recorded in the lower half of the table we see how the clearances of creatinine and inulin, which prior to the

Table 2.

Effect of elevated plasma creatinine and of phloridzin on creatinine/inulin clearance ratio in chimpanzee «Lucy» ♀ Surface area 1.19 sqm. Sodium amytal 90 resp. 65 mg per kg. *Italicized figures*, right bottom corner, give glucose/inulin clearance rate.

Pe- riod	Elapsed time minutes	Urine cm ³ / min.	Plasma mgm per cent			Clearance		Clearance ratio creat./inul.
			Inul.	Creat.	Glucose	Inul.	Creat.	
	From 2—8 min. 8 g Inul. + 1.2 g Creat. + 50 cm ³ H ₂ O intra- venously. 10—188 min. 5 % Inul. + 0.5 % Creat. + 0.8% NaCl intravenously, 3—5 cm ³ per min.							
1	60— 90	1.3	152	13.2	—	72	90	1.25
2	90—107	1.5	158	14.1	—	73	89.8	1.23
	5 % creat. added to infusion fluid at 107 min.							
3	134—150	5.4	178	74.5	—	99	94	0.95
4	150—172	6.0	183	90.0	—	96	96	1.00
5	172—186	6.4	181	101.1	—	93	93	1.00
	Creatinine-free infus fluid returned at 188 min.							
6	238—256	3.1	165	44.4	—	97	117.4	1.21
7	287—305	2.3	164	30.0	—	92	121.4	1.32
	<i>Effect of Phloridzin</i> 2—7 min. 8 g Inul. + 1 g C at. + 50 cm ³ H ₂ O intravenously. 10 min. o end as above.							
1	27— 62	3.2	88	9.4	—	108	131.8	1.22
2	62— 82	4.7	136	11.7	—	114	144.8	1.27
3	82—100	4.8	153	13.2	—	106	131.4	1.24
	30 g Glucose in 250 cm ³ H ₂ O per os, 4 g phloridzin intravenously at 102—117 min.							
4	132—150	13.3	170	16.3	153	66	70.6	1.07 (0.93)
5	150—168	10.0	175	17.4	138	66	70	1.06 (0.94)
6	168—185	8.1	178	18.2	124	68	69	1.02 (0.92)
I	II	III	IV	V	VI	VII	VIII	IX

phloridzination relate to each other as 1.22—1.27 to 1, come very close to one another during phloridzination and even become almost identical in the last determination.

Now, the mere fact that a difference between two objects A and B disappears gives in itself no clue whatever for deciding *whether* A approaches B, or *whether* B approaches A, or whether both A and B approach each other so as finally to coincide. Nor can any clue to this question be derived from the absolute magnitude of the creatinine and inulin clearances, because they are both far too variable for it being possible to say, whether their equalisation is due to absolute increase of the one, or to absolute decrease of the other. Thus, their equalisation in periods 3—5 of the first experiment of table 2 is not due to absolute falling off of creatinine clearance, because the latter is, absolutely, at least quite as low in periods 1 and 2, where the usual difference between the inulin- and creatinine-clearances is fully maintained. Nor can the equalisation of the two clearances in period 3—5 be derived from absolute increase of the inulin-clearance, as is evident from periods 6 and 7, where the inulin-clearance again is lower than creatinine clearance, although of quite the same absolute order as in periods 3—5.

Secondly, the phloridzin-experiment in the lower half of the same table demonstrates in still another way the impossibility of using the absolute order of the two clearances for deciding, whether their equalisation is due to the inulin-clearance approaching the clearance of creatinine, or versus. We see, that the inulin clearance falls off during phloridzin from 106 à 114 to 66 à 68, while the creatinine clearance falls from 131—145 to 69—71, i. e. the two clearances are cut in half, or nearly so. This absolute reduction of the clearances is, as a matter of fact, attributed by the authors to disturbances in renal circulation with consequent reduction of glomerular filtration. The volume of the glomerular filtrate possibly becoming reduced, the *filtered amounts* of both substances will be reduced in the same proportion, but a somewhat greater absolute reduction of *total clearance* will result for creatinine than for inulin *quite irrespectively of whether* phloridzin abolishes an earlier creatinine excretion in the tubules *or* an earlier inulin reabsorption; in the former case phloridzin neutralizes a factor making for a higher total creatinine clearance than corresponds to the filtration, in the second case it neutralizes a factor making for a lower total inulin clearance than corresponds to filtration. The impossibility of inferring anything from the absolute reduction of the clearances in the tabulated experiment is obvious already from the fact, that phloridzin by no means always causes the creatinine-clearance to fall off in absolute magnitude. Though frequently met with according to Smith and Clarke, no appreciable reduction of creatinine clearance is thus apparent in any of Poulsson's phloridzin experiments.

It is but right to point out, that Smith and Clarke have drawn no inferences from the absolute reduction of the inulin and creatinine clearances

in their phloridzin experiments. I have mentioned the matter here merely in the interest of completeness of discussion.

Further evidence is thus essential in order to enable us to decide, *whether the discussed equalisation of the creatinine and inulin clearances* is due to inulin clearance being raised relatively to creatinine clearance by phloridzin stopping inulin resorption in the tubules or due to creatinine clearance being relatively lowered by phloridzin stopping hypothetical creatinine excretion in the tubules. It is thus a grave and obvious logical error when the authors from the above utterly equivocal observations »conclude, that tubular excretion of creatinine occurs in the chimpanzee», and that phloridzin paralyzes this tubular excretion of creatinine, which neither has been shown to exist nor rendered in the least likely. A further grave error is committed, when Smith and Clarke »extend» the first of these conclusions »with confidence to the orang-utan and with a high degree of probability to the gibbon», no reason being given for this except a brief reference to the fact that creatinine and inulin clearances differ as much in these animals as in the chimpanzee before phloridzin! (cf. p. 136 of the quoted paper).

* * *

We have already remarked upon the curious omission of all reference to creatinine in Smith's statements to the effect that phloridzin equalizes the clearances of glucose, xylose and other carbohydrates with inulin clearance (cf. p. 130); we have also pointed out that this equalisation, contrary to the tenor of Smith's argumentation, constitutes no reason whatever in favour of inulin being a better gauge of glomerular filtration than creatinine, as phloridzin also renders the clearances of inulin and creatinine equal (cf. p. 132), *thus rendering all these clearances identical*, even when they differed prior to phloridzination. Smith's conclusions derived from the phloridzin experiments are thus altogether conjectural and based on no fact that does not go at least equally well with the contrary view, i. e. that part of the filtered inulin is resorbed and that no creatinine is excreted in the tubules of such species where the two clearances differ. Indeed, *the last view conforms to a most important scientific rule*, whereas Smith's conclusions quite deviate from it, namely the rule *that similar phenomena*

should be interpreted similarly in so far as no special reason against doing so is apparent.

As a matter of fact, it is evident from the above and is without reservation agreed upon also by Smith and his co-workers, that *phloridzin prevents tubular reabsorption of glucose, xylose and several other sugars*, and that this causes their clearances, which originally are lower than that of creatinine, to equal the latter. Now, as *phloridzin* has precisely the same effect on the clearance of the carbo-hydrate inulin in these species where its clearance is lower than the creatinine-clearance, namely to render it identical with the latter, Smith's very different interpretation does not conform to the rule mentioned, as long as no acceptable reason for neglecting it has been submitted.

This rather arbitrary mode of interpreting corresponding effects of identical experimental procedures becomes especially striking when applied to the results of one and the same experiment. Thus we see at the bottom of table 2, page 134 that *phloridzination* of the chimpanzee renders inulin clearance almost identical with creatinine clearance (creat./inul. clearance rate 1.02—1.07 as against 1.22—1.27 prior to *phloridzin*). Glucose clearance is at zero level prior to *phloridzination* and then rises to very near inulin-clearance (to 92—94 % of in. clear.). This approach of the glucose-clearance to the level of the inulin- and creatinine-clearances under *phloridzin* is described by Smith as «*Phloridzin blocking the tubular reabsorption of the glucose*», whereas the similar approach of the inulin- and creatinine-clearances is interpreted thus: «*phloridzin abolishes this tubular excretion of creatinine*». No reason is given for these different modes of interpretation.

* * *

The possibility of some of the filtered inulin being in some species reabsorbed by the tubules cannot be pushed aside merely by the contention that inulin is too inert a carbohydrate for being reabsorbed. Xylose and sucrose are by no means highly active substances chemically, require as a rule to be split up in simpler components during biological reactions, are indeed described as «*inert sugars*» by Smith himself, and were at first held by him not to be resorbable at all in the renal tubules (Smith, *Physiol. of the Kidney*,

p. 11). The inertness of inulin, which is a colloid starch-like carbohydrate, is no doubt more marked than that of xylose and sucrose, and this may well account for its tubular irresorbability in a good number of species (frog, dog, sheep, seal, rabbit). The organisms of different species often treat various carbohydrates somewhat differently, and inulin being by no means absolutely inert, there is, however, no a priori reason against inulin being somewhat resorbable in the tubules of other species. This possibility is so much the more to be borne in mind, as inulin hydrolyses into that excellently resorbable sugar, fructose. Hydrolysis of inulin is generally stated to be the easiest way in which to obtain fructose artificially and such hydrolysis is the fundamental chemical procedure in the determination of the inulin concentrations of blood and urine in the inulin test. How can we be sure, that some degree of inulin hydrolysis is out of question in the renal tubules of every species? How can we, in the absence of all evidence to the contrary, rule out this hydrolysis, when we know the tubular urine to be subjected to manifold and considerable chemical changes during the tubular transformation of glomerular filtrate into as a rule very differently composed urine, and when we know the tubular cells to be electrically charged with positive and negative potentials of measurable strength and of exceedingly strong effect over the immeasurably short interdistances between the tubular cells and the constituents of the urine on their surface? (Ekehorn, *Über d. integrat. Natur d. normalen Harnbildung*, Chapters 35—38: *Über die Biophysik d. Kanälchenresorption*.)

* * *

The effect of excessive plasma creatinine.

Returning to table 2 page 134, we will now consider the experiment recorded in the upper half of the table (effect of elevated plasma creatinine) which presents reasons for far more serious criticism than any of the experiments and views already considered. Our remarks have hitherto hardly gone beyond the points, *that* Smith and his collaborators *have failed* to substantiate their view of inulin not being reabsorbed *and* of creatinine being in part secreted by the tubules (in those species where creatinine clearance is greater than that of inulin), *and that they even have failed* to submit any experiment rendering the opposite view in the least un-

likely or improbable. Our succeeding remarks on the effect of elevated plasma creatinine, however, will go a step further and show, that Smith's above mentioned view and some of its alleged implications run quite contrary to several experimental facts.

We see from table 2 that elevation of plasma creatinine in the chimpanzee to 75 mg per cent or more causes the clearances of creatinine and inulin to equal each other, whereas their earlier ratio in this experiment is 1.21—1.32 to 1.00.

Incidentally, we cannot omit to point out the altogether conjectural nature of the author's immediate conclusion (Smith & Clarke, Amer. J. Physiol. 1938, vol. 122, p. 132—139), namely that this equalisation of the clearances indicates that the (normal) difference between the clearances is due to tubular excretion of creatinine as the authors have not considered at all and still less ruled out another way of accounting for the observed phenomenon, to which we will return on page 150 below.

We will compare the above experiment with an *alleged general law for tubular activity*, on which Smith and his co-workers lay much stress, namely that «when the plasma concentration of creatinine is raised above a certain critical level the tubular mechanism becomes saturated, so to speak, and excretes the substance at a maximal »rate« (Smith, Physiol. of the Kidney, p. 22.) Even in this concentrated book much space is given over to describing and explaining a number of factors to be used in the mathematical formulas said to express this law, and much space is also given over to show how this law applies to tubular resorption as well as to tubular excretion. The same is also true of Shannon (Shannon: Renal tubular excretion, Physiol. Rev., 1939, vol. 19, p. 63—93.) who devotes a third of his paper to explaining «the mechanism of tubular excretion» in accordance with this law, and who submits a great number of mathematical formulas alleged to express the law and its implications quantitatively.

There is no need to enter into either the primary formula¹ or

$$A + B \rightleftharpoons AB \rightleftharpoons T_s + B$$

into the various complicated formulas further derived from the first one. It is indeed obvious both from the formulas as such and from the whole tenor of Shannon's exposition, as well as from a

¹ A is the amount of solute on the proximal side of the excretory or reabsorptive reaction, B is the cellular element effecting excretory or reabsorptive transport, and T_s the amount of solute transported to the distal side of the reaction.

Table 3.

Period	Creatinine in plasma mg per cent	Total amount of excreted creatinine, mg per minute.	Amount of filtered creatinine according to Smith, mg per minute.	Amount of creatinine secreted by the tubules, according to Smith, mg per minute.
1	13.2	11.9	9.5	2.4
2	14.1	12.7	10.3	2.4
3	74.5	70.	73.8	—3.8 (sief)
4	90.0	86.4	86.4	0
5	101.0	93.9	93.9	0
6	44.4	52.1	43.1	9
7	30.0	36.4	27.6	8.8

great number of particular remarks, that these formulas are intended to represent quantitatively and in accordance with the said »law» the activities of tubular secretory and reabsorptive mechanisms. This is clearly indicated by Smith (Smith, Kidney, Ann. Rev. Physiol., 1939, 1, p. 506). »One of the most notable advances in the problem of tubular excretion and resorption has been the study of the kinetics of these processes. *In every instance in which this problem has been examined, it has been found that the quantity of solute excreted or reabsorbed by the tubules per unit time increases with increasing plasma concentration until a constant maximal rate is reached, which is thereafter maintained* as the plasma concentration is raised to higher levels» (all italics by me). Again, in Smith's Physiology of the kidney, p. 22, we read »In every instance, where an adequate examination has been possible, it has been shown that — — — in tubular excretion as in the case of tubular resorption there exists a limitation of tubular activity which takes the form of a maximal rate of excretion».

These opinions contrast strikingly with the data from the first experiment of table 2. We can calculate *the amounts of creatinine alleged to be secreted* by the tubules by subtracting *the amounts alleged to be filtered* in the glomerules (the products of creatinine conc. in plasma and alleged volume of filtrate-fluid, indicated according to Smith by inulin clearance) from *the amounts actually excreted* (the products of creatinine clearance and plasma concen-

tration of creatinine). The figures of table 3 on page 140 are thus obtained for the resp. 7 observations of the experiment.

We see that the alleged tubular excretion of creatinine certainly may rise with increasing plasma concentration (cf. periods 1 & 2 with 6 & 7); but *these figures are quite contrary to the idea of the alleged tubular excretion attaining a maximal rate which is thereafter maintained* (cf. quotation above). Irrespectively of whether the alleged maximal rate has been reached in periods 6 & 7 (plasma creatinine 30 a 44 mg per cent) or whether it still remains to be attained, it is obvious that even the alleged tubular excretion of periods 6 & 7 (8.8 a 9 mg creatinine) is *not maintained* at the higher levels of plasma creatinine in periods 3—5, where no tubular excretion of creatinine occurs at all. Indeed, there remains in periods 3—5 no trace even of the tubular excretion of periods 1 & 2, which certainly is far below the alleged maximum.

This extraordinary discrepancy between alleged and real experimental results (cf. the statement *in every instance etc.*, quoted above) cannot possibly be repaired in future publications by some such statement as the alleged maximal tubular excretion not being large enough to be discernible when very much creatinine is filtered at high plasma levels. When amounts of 2.4, 8.8 and 9 mg creatinine, alleged to have been secreted tubularly, are clearly discernible when the total creatinine excretion varies between 11.9 and 52.1 mg, why should not an amount that equals or surpasses 9 mg be discernible at total outputs of 70—90 mg?

We find, of course, the same discrepancy also if we compare the clearances without taking the trouble to compute the amounts of creatinine excreted by the whole kidney or alleged to have been secreted in the tubules. Identity of creatinine and inulin clearances (periods 4 & 5) implies in Smith's own parlance *identity with glomerular filtration* and there is no place here for any additional tubular excretion of creatinine still less for one functioning at its maximal rate. Indeed, the fact that creatinine clearance in experiment 3 is *less* than inulin clearance (cf. table 2, page 134 above) and that more creatinine thus has been filtered than excreted into the urine (cf. exper. 3, table 3, p. 140) indicates strongly a very different explanation of the facts observed, namely that creatinine clearance decreases at excessive plasma levels because the tubules are no longer able to retain all the filtered creatinine as normally (cf. below p. 150 & table 4, p. 146).

Nor is it possible to explain away this experiment No 3 as merely due to experimental errors, the «resorbed» quantity of creatinine being over 50 % greater than the quantities alleged to be secreted by the tubules at the distinctly hypernormal creatinine levels of exper. 1 & 2, and consequently very much more in excess of the amounts of creatinine alleged to be tubularly secreted at more normal levels, on which latter Smith builds so many conclusions.

These extraordinary discrepancies *negative completely the central point of the laws and formulas* of Smith & Shannon, alleged to explain tubular secretory or resorptive activities in quantitative terms.

It is of special interest to find these laws negated just in respect of the alleged tubular secretion of creatinine in the primate kidney. The alleged superiority of inulin over creatinine in tests ad modum Rehbergi is, in fact, altogether based on the idea of creatinine being secreted in the tubules of such species, where the creatinine clearance surpasses inulin clearance. Among such species, apes and man are incomparably more suitable than the rest for experimental examination of these matters.

It is thus no doubt rather surprising, that Smith appears to foregoe all reference to the above experiment on the effect of elevated plasma creatinine in the chimpanzee, when he in other papers discusses the validity and bearings of his «kinetic» laws and formulas regarding the alleged tubular excretion of creatinine. Instead he bases his discussion on experiments on chicken and fishes, which present no advantages but instead many special difficulties in the case of comparative clearance studies (cf. p. 155).

Most astonishing is also Smith's sweeping assertion in his more comprehensive publications, namely that his «kinetic» laws and formulas have been verified in every examined instance (cf. p. 140). That elevation of plasma creatinine in the chimpanzee in no way causes the alleged tubular excretion of creatinine to continue at a «constant maximal rate» is indeed evident not only from our above remarks but also from Smith's own words in the summary of his special paper. «It is demonstrated in the chimpanzee that elevation of the plasma level of creatinine depresses the creatinine-inulin clearance ratio towards unity», i. e. every sign of the alleged tubular excretion of creatinine disappears (Smith & Clarke, *Am. J. Physiol.* 1938; vol. 122; p. 138).

Clearance depression at elevated plasma levels is no characteristic of tubular secretion.

Both the idea of a part of urinary creatinine being excreted by the renal tubules in species exhibiting a creatinine clearance larger than that of inulin, and the idea of excessive plasma creatinine saturating this tubular excretory mechanism and thus preventing its activity to increase above a certain maximal rate — both these ideas, however, are definitely negatived by the experiment now to be discussed (Kay and Sheehan, Renal elimination of injected urea and creatinine, *J. Physiol.*, 1933, vol. 79, p. 359—415.). A very marked reduction of creatinine clearance follows in fact upon elevation of the plasma level of creatinine, yet the animals experimented on here are *rabbits*, i. e. one of those animals where, according to Smith and his own co-workers, creatinine and inulin clearances always are equal at the outset and where any tubular secretion of creatinine therefore is out of question; cfr. Smith's statement, referred on p. 6. above, »that in these species both substances (inulin and creatinine) are excreted by (glomerular) filtration without tubular participation.»

The experiments in question are described and tabulated on p. 389 of Kay & Sheehan's paper. The experiments do not record clearances directly but instead the renal extraction rates of injected urea and creatinine, and this necessitates some preliminary discussion here.

The Renal Extraction Rate is defined as the percentage proportion between the amounts of a urinary constituent actually excreted by the kidneys during a certain period of time *resp.* contained in the volume of blood simultaneously supplied to the kidneys. Thus

$$\text{R.E.R.} = \frac{U \cdot C_u}{B \cdot C_b} \cdot 100 = \frac{100}{B} \cdot \frac{U \cdot C_u}{C_b}$$

U and B are here the volumes of the urine *resp.* of the renal blood, and C_u and C_b are the urine and blood concentrations of the urinary constituent in question.

As $\frac{U \cdot C_u}{C_b}$ denotes this substance's clearance, Cl , we may write,

$$\text{R.E.R.} = \frac{100}{B} \cdot Cl$$

That is, the *R.E.R.* of a certain urinary constituent is directly proportional to the clearance of this substance.

As it is a difficult and complicated task to determine the volume *B* of the renal blood, the *R.E.R.* is best determined from the concentrations of the examined substance in samples of renal vein-blood and of arterial blood (usually heart blood). For creatinine the *R.E.R.* is thus

$$\text{R.E.R.}_{Cr} = 100 \frac{\text{diff. betw. creatinine conc. of heart \& renal vein blood.}}{\text{creatinine conc. of heart blood}}$$

The difference in creatinine concentration between heart and renal vein blood denotes obviously the amount of creatinine removed from the unit volume of blood passing through the kidney. Dividing this amount

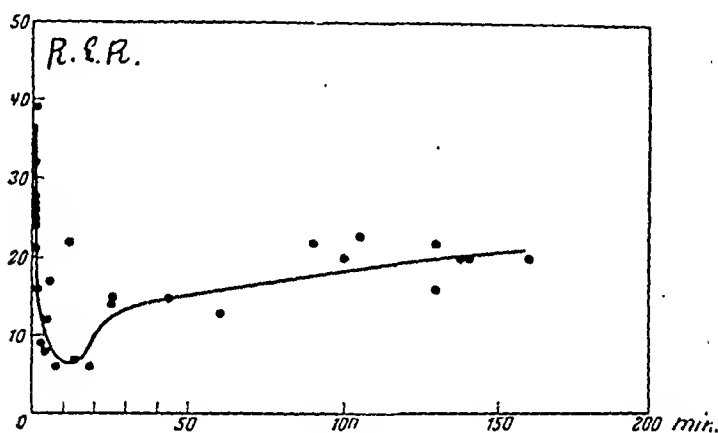


Fig. 1.

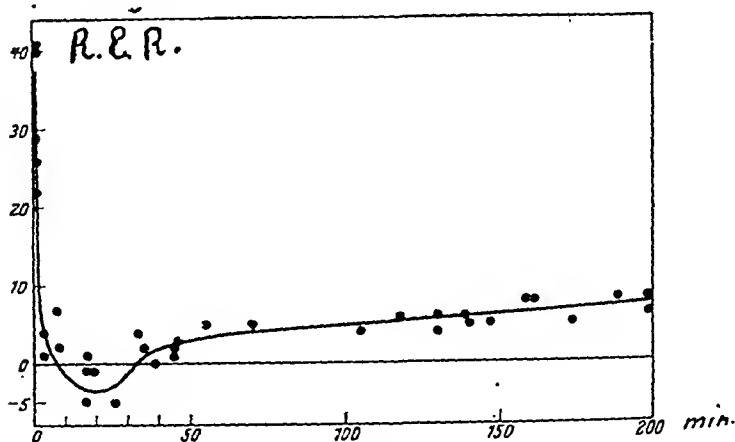


Fig. 2

by the amount of creatinine present in the unit volume of arterial blood, we obviously find the R.E.R.

Now, it is essential to observe *one condition* in experiments of this type, namely not to withdraw the sample of renal venous blood until a fair time has been allowed to pass after an injection into the blood of a substance, the R.E.R. of which is to be determined.

A very high proportion of an injected substance disappears from the blood immediately after the injection because of diffusion out into the lymphatic spaces etc. of the organs, and the difference between arterial and renal venous blood will be very much higher than what corresponds to the renal excretion of the substance. This phase passes off in about 3 minutes or less; it is followed by another phase, when the depositions of the substance in the lymphatic spaces etc. of the organs gradually return to the blood; this second phase is very much less abrupt than the first but instead lasts longer, and venous kidney blood removed during this time will show a lower rate of extraction than corresponds to the amount of the substance actually excreted into the urine. In the case of *f. inst.* urea the apparent extraction rate may indeed become negative during this second phase, the venous kidney blood actually containing a higher percentage of urea than arterial blood. This second phase is well over in about one hour, usually even somewhat earlier.

The two figures from Kay and Sheehan on the preceding page show both the above mentioned phases very clearly. The upper figure refers to apparent and real R.E.R. of creatinine after injection into the blood of rabbits, the lower shows the same for urea after urea-injections. The real R.E.R., i. e. the R.E.R. determined from blood from the kidney vein withdrawn an hour or later after the injections, are in rabbits about 20 % for creatinine and about 5—8 % for urea, figures altogether verifiable in other ways as well (Ekehorn, Über die Bedeutung renaler Ausschwemmungsgrade, Virchow's Archiv, 1935, 295, p. 256—89).

Neglect of the essential condition of not taking samples of renal venous blood too early after injections of substances into the blood will seriously upset the inferences drawn from R.E.R. experiments, but no such objection can be levelled against R.E.R. experiments where blood samples are taken and other operations performed *first 112—160 minutes* after the injections into the blood, as was the case in the experiments under discussion here.

Two sets of experiments were performed. In one set (series F) the rabbits received intravenously a mixed solution of 1000 mg urea and 250 mg of creatinine per kg body-weight; in another series (series G) the rabbits received intravenously no urea but 1.6—2.0 g creatinine per kg body weight. The results are given below:

Table 4.

Rabbit	Urea mg per cent		Creatinine mg per cent		Renal Extr. Rate	
	Heart blood	R. vein blood	Heart blood	R. vein blood	urea	creatinine
F ₁	147.6	139.2	18	14	6	22
F ₂	95.7	92.1	8.2	6.9	4	16
F ₃	111.2	104.1	9.3	7.5	6	20
F ₄	95.9	91.5	7.1	5.7	5	20
F ₅	119.9	110.6	10.4	8.3	8	20
Average	114.1	107.5	10.6	8.5	5.8	19.6
G ₁	38.1	37.9	240	222	0	8
G ₂	50.1	48.9	141	123	2	13
G ₃	48.4	48.4	105	97	0	8
G ₄	24.9	24.3	84	69	2	18
Average	40.4	40.	142.5	128	1.0	11.75

We see that the Renal Extr. Rates of both urea and creatinine remain quite normal in series F, but that R. E. R. falls markedly in series G for both urea and creatinine. We will later return to the large decrease in the R. E. R. of urea in series G. As to the decrease here in the R. E. R. of creatinine it is to be noted, that quite similar figures ranging between 8 and 16 were obtained in other series of experiments, not included in the above table, where blood creatinine was brought up to similarly high levels.

The average R. E. R. of creatinine amounts in series G exactly to 60 % of the average R. E. R. of series F, and average creatinine clearance in G will obviously fall to 60 % of the average clearance in F, when only 11.75 % instead of the ordinary 19.6 % of the creatinine contained in the unit volume of renal blood is removed from the latter during its passage through the kidney.

Such decreases of the clearance of urinary constituents consequent upon excessive elevation of their plasma concentrations are regarded by Smith and his followers as exceedingly important phenomena, alleged to be highly characteristic of tubular secretion. Røjel (Nyrernes tubulære sekretion, Nordisk Medicin, 1943, vol. 20, nr 46 p. 1919) embraces Smith's ideas unreservedly and states that

»Self depression of clearance depends on tubular secretion being an active cellular process with a certain maximal limit of function like all other physiological processes. Once the maximum of secretory tubular function has been reached at a certain plasma concentration, secretion remains constant at further elevation of the plasma level of the substance in question. Glomerular filtration behaves quite differently; filtration is a purely physical process and is therefore proportional to the volume of the filtrate and to the plasmatic concentration of the substance. Hence it is obvious, that the filtered amount of the substance must be very large at plasma concentrations above the level corresponding to maximal tubular secretion, whereas the secreted amount will remain constant; clearance will therefore decrease with still higher elevation of the plasma concentration and will approach the figure cleared solely by glomerular filtration» etc.¹

Indeed, this »self-depression of clearance» at high plasma levels is regarded as so characteristic of tubular secretion, that decrease of a substance's clearance at high plasma concentrations is expressively stated to be a decisive proof that this substance is secreted by the renal tubules (cf. Röjel, p. 1920).

All these ideas are altogether negatived by the rabbits of series F and G, as tubular secretion of creatinine is quite out of the question here, according to Smith himself, and as elevation of the plasma creatinine nevertheless causes a most conspicuous depression of creatinine clearance.

The reduction of the Renal Extr. Rate to 60 % of its normal order represents a depression due to disturbed relations between the creatinin and the renal parenchyma. In addition to this depression, however, the creatinine-clearance falls off still further because of the poor renal circulation in series G.

The last formula of page 143 may be written thus:

$$Cl = (R.E.R.) \cdot B \cdot \frac{1}{100}$$

The average renal bloodflow in series G amounted only to $9/23 = 39\%$ of the average bloodflow in series F, which was of altogether normal order (p. 150).

If the factor R.E.R. decreases to 60 % and the factor B to 40 % of their former values, their product (the clearance), will obviously fall off to

¹ Translated from Danish by Ekelhorn.

$6/10 \cdot 4/10 = \frac{1}{4}$ of its former value. The creatinine-clearance must obviously fall off most considerably when (I) the volume of the renal blood is much reduced, and when (II) each cubic centimetre of this blood is cleared of a considerably lower fraction of its creatinine than normally.

As elevation of the plasma creatinine in Smith's experiment has not been accompanied by any reduction, absolute or relative, of the clearance of inulin (table 2, p. 134), the renal blood-flow has probably been very much the same before and during the period of elevated plasma creatinine in Smith's chimpanzee. Therefore, we have not believed ourselves justified in comparing Smith's results with the whole clearance-depression of the rabbits of series G, but only with that part of this depression that is independent of the reduced volume of the renal blood.

Even so, the depression of the creatinine clearance after elevation of the plasma creatinine is far stronger in our rabbits than in Smith's chimpanzee, where the depression is only relative, i. e. where creatinine-clearance merely becomes reduced to equality with inulin clearance but still remains as high, absolutely, as prior to the elevation of the plasma creatinine (cf. table 2, p. 134). In the rabbits of series G creatinine clearance, on the other hand, becomes reduced to 60 % of its former value, and if we take account of the lessened renal blood flow, even to 25 %, on an average.

These results, showing how creatinine clearance, or strictly speaking a factor proportional to creatinine clearance, decreases very considerably on creatinine being brought to excessive plasma levels, derive their interest not merely from the fact, that it is impossible in rabbits to explain this decrease from any kind of tubular creatinine excretion reducing its output absolutely or relatively; as already mentioned, tubular excretion of creatinine is entirely out of the question in rabbits, this even according to the views of Smith and his co-workers.

Now, the above results are also of interest because they give a very definite clue to the cause of creatinine clearance decreasing when plasma creatinine is excessively high. This phenomenon, in fact, must be due *either* to the relative rate of glomerular filtration decreasing, i. e. to subnormal quantities of glomerular filtrate being formed out of the unit volume of renal blood, *or* to the tubules being unable to retain the whole of the filtered creatinine in the urine as they normally do. There is, indeed, no further way in which the said phenomenon could possibly occur in rabbits, where the urinary creatinine even according to Smith is eliminated from the blood solely by means of glomerular filtration.

As to possible partial diffusion of filtered creatinine through the tubular walls back into the blood, we have to recollect that most of the water of the glomerular filtrate is reabsorbed by the tubules, so that usually only about 1 % of the filtered water escapes into the bladder, which fraction may increase up to some 10 % in very strong water diuresis and up to 15—20 % in excessive diuresis. This implies corresponding increases in concentration of filtered substances retained in the urine, and the urinary concentration of creatinine is thus always several times a multiple, and as a rule a very high multiple of its plasma concentration. The conc. of urine creatinine is usually a 100—150 fold and even in excessive water diuresis still a 7—10 fold multiple of creatinine conc. in plasma. (cf. tables 1 & 2, *Über die integrat. Natur d. normal. Harnbildung*, p. 172). Urinary concentration of creatinine rising like this, when plasma creatinine is normal (below 2 mg per cent) or is merely brought up to 4—7 mg per cent as in the tables just quoted, urinary creatinine would obviously become concentrated to such excessive levels in experiments with plasma creatinine at 80—240 mg per cent (cf. above the tables on p. 134 and 146) that a critical point may well be reached, where the renal tubules are unable to hold back all the urinary creatinine as usual.

However marked a physiological characteristic may be, as f. inst. the normal impermeability of the tubular walls to creatinine, yet such characteristics are never absolute in the strictest sense of the word, nor are they entirely unaffected by excessive stress, and they may break down at least partially during highly unphysiological conditions.

The idea of partial escape of filtered creatinine through the tubular walls under abnormal conditions receives strong support from the observations already mentioned (cf. p. 118 above), namely that, when the vitality of the tubular epithelium has become seriously lowered in advanced stages of glomerulo-nephritis, fractions of the filtered creatinine diffuse back into the blood through the tubular walls already at normal or sub-normal concentrations of urinary creatinine. (Cfr. below p. 154; toxic injury to the tubular walls because of the excess of plasma creatinine in the experiments discussed).

Curiously enough the same idea is accepted also by Smith, although in quite another connection. Referring to certain experiments by Forster, Smith states (Smith, *Kidney*, p. 510, *Ann. Rev. Physiol.*, 1939, vol. 1, p. 503—28. Forster, *J. cell. comp. Physiol.*, 1938, vol. 12, p. 213) that «in the phloridzinised frog the glucose, xylose, and creatinine clearances are identical, but are all below the inulin clearance, indicating that although phloridzin blocks the active reabsorption of glucose and xylose in this animal, it has also the effect of altering the tubules so as to permit back diffusion (about 12 %) of small molecules.» Inulin and creatinine clearances however, are identical in unphloridzinised frog, «indicating identity with the glomerular clearances» (Smith, *Kidney*, p. 507; Forster as above); this fact places the frogs in the same group as rabbits, dogs, seals and sheep, i. e. among animals where tubular excretion of creatinine is out of

the question, and no absolute or relative change of any such tubular excretion can therefore possibly be suggested in explanation of a decrease in creatinine clearance. It is of considerable interest to find Smith himself then adopt the view that the decrease of creatinine clearance is due to the phlorizinised tubules having become unable to retain it quantitatively as usual in the urine of frogs; therefore part of the filtered creatinine diffuses back into the blood through the tubular walls. *On the one hand* this interpretation removes all possibility of Smith objecting against my interpretation of the observations on rabbits discussed here, *on the other hand* it is not clear, why Smith has not taken these experiments on frogs into consideration in explaining those of his experiments where creatinine clearance is alleged to have become depressed by means of raising plasma creatinine to abnormal levels, especially as exper. 3 of tables 2 and 3 strongly suggests resorption of part of the filtered creatinine, as just mentioned above.

* * *

Returning now to table 4 on page 146, it is easy to demonstrate positively, that the tubular walls have become abnormally permeable and that they have allowed abnormal escape of filtered substances from the urine.

We recollect from page 148, that the low R. E. R. could derive also from another cause, namely from *subnormal amounts of glomerular filtrate being produced from the unit volume of renal blood*. The possibility of such a reduction of the relative rate of glomerular filtration having occurred in Series G cannot be precluded, as the excessive rise of the level of the plasma creatinine was accompanied by considerable changes of the renal bloodflow, which ranged in Series G between 0.8 and 1.2 cm³ per minute and gram kidney weight, averaging 0.9 cm³, as against the normal volume of renal blood in Series F ranging between 1.6 and 3.1 cm³ with an average of 2.3 cm³ per minute and gram kidney weight.

It is, of course, impossible to deny, that this difference in the volume of renal blood *might* have been accompanied by other haemodynamic changes as well, which perhaps have caused the relative filtration rate to fall. This question must be left open, as the experiments of series F and G contain no data enabling us to compute the absolute volumes of glomerular filtrate produced.

We must not believe, on the other hand, that glomerular filtration necessarily reflects the volume of the blood passing through the kidneys. It suffices to refer to table 21 of my monograph (Ekehorn, Über die integr. Natur d. normalen Harnbildung, table 21 p. 493—94; the table is

extensively discussed on pages 476—96). A very extensive series of experiments are recorded here, where the volumes of the renal blood differed at least as much as in the series F and G, and where most considerable differences as to other haemodynamic and filtrative factors must have occurred as well. The quoted table 21 refers to dogs, one kidney of which had been deprived of its nerve-supply as completely as possible. In spite of this, the *absolute rates* of glomerular filtration, i. e. absolute volumes, were equal throughout the whole series in the two kidneys of each animal, which obviously implies, that the *relative filtration rates*, i. e. the amount of filtrate produced from the unit volume of renal blood, were *higher* in the kidneys with the lesser than in the kidneys with the much larger blood supply. This in every respect very remarkable experimental series was originally performed by Marshall jr and A. C. Kolls (Marshall & Kolls, Amer. J. Physiol., 1919, vol. 49, p. 302—16). The accuracy of the determinations, from which the above datas on glomerular filtration are deduced, is discussed on p. 498—503 of my monograph and found to be very high especially as the filtrative rates were determined from the excretion rates of several substances as well as from creatinine.

As to the rabbits of Series G we can state quite positively, however, *that whatever change that may have occurred in the absolute or relative rates of glomerular filtration, it falls definitely short of accounting for the reduction of the Renal Extraction Rates.* The R. E. R. of urea could not possibly have fallen from the normal average of 5.8 in Series F to the average of 1 in Series G without the renal tubules having become more permeable to substances diffusing away from the urine.

Unless a higher fraction of the filtered urea escapes through the tubular walls in Series G than normally and in Series F, the Renal Extraction Rate of urea could not have become reduced more than the R. E. R. of creatinine. In other words, *if the volume of glomerular filtrate in Series G amounts to on an average 11.75 % of the volume of the renal blood instead of 19.6 % as in Series F, then filtered urea in Series G must amount to 11.75 % of the total urea of the renal blood instead of 19.6 % as in Series F, since the amounts of filtrable blood constituents in the whole renal blood resp. in the glomerular filtrate are proportional to the volumes of blood and filtrate, their concentrations being the same in both fluids.*

Now, when in series G *at least 11.75 % of the urea contained in the renal blood is filtered in the glomeruli, at least nine tenths of the filtered urea have obviously diffused back into the*

blood through the tubular walls, when on an average but 1% of total renal blood urea is retained in the urine.

I have italicized *at least* above, because if creatinine has escaped from the tubular urine back into the blood in series G, i. e. if creatinine thus has been filtered in excess of the 11.75 % of total blood creatinine passing into the urine, *more than 11.75 % of total renal blood urea* must have been filtered in the glomeruli, and the 1 % of total renal blood urea retained in the urine therefore represents a lesser fraction of filtered urea than one tenth; more than nine tenths of filtered urea has diffused back into the blood.

This is an escape from the urine of a considerably higher fraction of filtered urea than in series F, where 19.6 % of the urea of the renal blood were filtered in the glomeruli, and where 5.8 % of renal blood urea or 3/10 of filtered urea were finally excreted.

The lessened ability of the tubular walls to retain the urea of the urine in series G becomes the more obvious if we take account of the very different concentrations of urine urea, consequent upon the very elevated blood urea in series F, and upon the normal blood urea of series G. Because of the much higher diffusion pressure of urea in the final urine of series F, retention of urea has been far more difficult from a physical point of view than in series G. Yet the tubular walls retain a three times higher fraction of filtered urea in F than in G.

We have confined our discussion to the average Renal Extraction Rates of the resp. Series F and G of table 4. The same mode of reasoning and calculation can, of course, be applied also to the data of the separate experiments of the series.

A glance at table 4 suffices to show one further fact. *The R. E. R. of creatinine is lowest* in the two rabbits G₁ and G₃ where the abnormal inability of the tubular walls to retain the urinary constituents is most marked, practically all the filtered urea having diffused back into the blood.

* * *

We can sum up our discussion of Series F and G thus:

1) These experiments negative definitely the view of Smith and his co-workers as to tubular excretion of a part of the urinary

creatinine in such species (man, apes, chicken etc.) where creatinine clearance surpasses inulin clearance. Decrease of creatinine clearance at excessive levels of plasma creatinine — which phenomenon Smith and co-workers regard as a most essential characteristic of the alleged creatinine excretion in the tubules — occurs in fact also in such species (f. inst. rabbits) where no tubular creatinine excretion exists, i. e. in species where the identity of the inulin and creatinine clearances in Smith's own words «indicates identity with glomerular clearances». The decrease may be much larger here than the decreases reported from the first group of animals.

2) Occurrence and magnitude of this decrease of creatinine clearance appears to depend on the degree of excess plasma creatinine. No decrease becomes apparent in rabbits until plasma creatinine reaches a level of over 80 mg per cent (rabbit G₄ table 4). In chimpanzees creatinine-clearance is distinctly normal at plasma levels of about 45 mg per cent and decrease is reported first for plasma levels of 75 mg per cent (page 134). Although different species and individuals may differ as to the plasma level of creatinine which cause decrease of creatinine clearance, the critical level is obviously high above all possible levels of plasma creatinine in Rehberg's test.

3) The magnitude of the decrease appears further, in spite of considerable individual variations, to depend roughly on the degree of plasma creatinine excess. Average plasma creatinine is almost twice as high in Series G as in the chimpanzee (cf. pages 146 and 140; 142 mg per cent resp. 88 mg in periods 3—5), and the decrease of creatinine clearance is much stronger in the rabbits of Series G than in the chimpanzee (pages 148 & 134).

4) Decreases of creatinine clearance at excessive levels of plasma creatinin thus having no foundation whatever in any phenomena of tubular excretion, such decreases must be due *either* to partial diffusion through the tubular walls of filtered creatinine back into the blood *or* to lessened relative rate of glomerular filtration, i. e. to lessened filtration from the unite volume of glomerular blood.

5) It is impossible to say definitely from the data concerning the rabbits of Series G whether the second of the above two causes has been in operation or not; it may have been, but nothing indicates that it actually has been operative.

6) Irrespective of, whether or not lessened relative rate of glomerular filtration has contributed to the results in Series G, *only the first cause* (imperfect retention of filtered creatinine within the tubules) suffices for explaining the results. Lessened ability of the tubular epithelium to withstand diffusion of urinary constituents back into the blood is, in fact, clearly demonstrable in every rabbit of Series G. That this must have led to part of the filtered creatinine escaping back into the blood is obvious at once, and is rendered still more evident by the fact that the creatinine clearance has decreased most just in those rabbits, where tubular ability to prevent other urinary constituents to pass back into the blood has been maximally lessened.

7) A tentative argument in favour of creatinine having some toxic effects when present in the plasma at levels of 75--240 mg per cent, i. e. at levels 50--200 times the normal, is contained in the fact that tubular retention of glomerularly filtered substances becomes imperfect in respect also of *other substances than creatinine* (urea). Creatinine does not diffuse away from tubular urine merely because its urine concentration rises to such high levels when plasma creatinine is so excessive. There must be some change in the tubular epithelium, otherwise urea could not diffuse away as it does in Series G. This is so much the more obvious, as we have no abnormally augmented escape of urea in Series F in spite of urea obviously having been contained in the urine here at much higher concentrations than in G (cf. table 4; observe that urea was raised to much higher plasma levels in F than in G, and that plasma creatinine was but moderately hypernormal in F). The idea that creatinine is toxic for the kidneys at the excessive plasma levels in Series G is further supported by the marked decrease in renal blood-flow reported here (cf. page 150).

Discussion.

The alleged superiority of inulin over creatinine in tests *ad modum Rehbergi* suffers already at the outset a most considerable restriction, as the clearances of inulin and creatinine differ, according to Smith himself, only in man, anthropoid apes, chicken and certain fishes. In frogs, dog, rabbit, seal and sheep the two clear-

ances are identical. Several species of monkeys are said to occupy an intermediate position between these groups. Identity of the inulin and creatinine-clearances, however, implies not only identical volumes of glomerular fluid, but implies also identical results as to all other data that may be calculated according to these methods; this is obvious from the way in which all these data are computed (cf. p. 117).

It is, of course, impossible to claim any superiority of one over another method in any of all those species where the two methods yield identical results.

* * *

Turning now to those species where the clearances of inulin and creatinine differ, we remark in the first place, that all information derived from man and apes is of incomparably greater interest and importance than information from birds and fishes. The latter can hardly claim more than a mere curiosity interest in clinical physiology, and they constitute rather a side issue even in general renal physiology.

Both birds and fishes, as a matter of fact, present further a number of very special problems. The necessity of collecting ureteral urine complicates all clearance tests considerably in birds and fishes.

In *birds* further problems hinge upon the fact that the urine is not fully elaborated when it leaves the kidney or indeed the ureters. Ureteral urine is abundant and as a rule hypotonic relatively to the blood (or sometimes slightly hypertonic); this urine is then subjected to intense water resorption and turned into a semisolid paste in the cloaca or the rectum. In the kidneys of *fishes*, the tubules are not always provided with glomeruli; aglomerular tubules may be rather numerous, and several species have only aglomerular tubules in their kidneys. Truly aglomerular tubules must necessarily have *secretory* functions, and they differ thus most markedly from mammalian tubules. In the mammalian kidney the tubules have, even on Smith's own hypothesis, *resorptive* functions in respect of all urinary constituents with lower clearances than inulin and creatinine, that is, in respect of water and all other biological constituents of the urine in health or disease. As mechanisms with different and, indeed, with quite opposite functions cannot be directly compared, the presence or prevalence of aglomerular tubules in fish kidneys renders it difficult or impossible to apply the information derived from renal experiments on fishes to mammalian kidneys.

There is a further reason, however, for concentrating our attention especially to man and apes in the case of species with diffe-

rent inulin- and creatinine-Clearances. This is the fact, that the difference between the two clearances is said to be very marked and regular in primates. Smith and co-worker's papers contain numerous statements to this effect. It is then exceedingly curious, that *average inulin Clearance*, as submitted by Smith himself for man, almost coincides with the generally accepted average clearance for creatinine.

As a matter of fact, Smith puts average inulin clearance at 125 cm^3 in man and average creatinine clearance at 175 cm^3 . There is no reason to dispute the representativeness of the *first figure* as an average. Hogeman in a recent paper (O. Hogeman, Inulin-clearance, Svenska Läkartidningen, 1943, vol. 38, p. 2253—2264.) obtains inulin averages of 121 resp. 118.6 cm^3 in two series of 20 resp. 15 swedish males with healthy kidneys. As a general average for his own cases and for those of the inulin literature Hogeman submits the figure of $122 \pm 20 \text{ cc/min}$.

Smith's second figure, 175 cm^3 , however, is too high for an average of creatinine in man. It shall be admitted at once that creatinine clearances of 175 cm^3 , and even more, are met with now and then, as is evident from the numerous tables of creatinine tests contained in my latest monograph (Ekehorn. Über die integrat. Natur der normal. Harnbildung). Thus, loc. cit. p. 172—73 we have two tables of together 35 creatinine determinations on healthy grown-up individuals, where this clearance (filtrate-volume) in one instance amounts to 200 cm^3 , although filtration otherwise always is below 150 and *averages* 131 cm^3 . Loc. cit. p. 221—226 are further tables of 209 creatinine tests on 59 patients (20 healthy + 24 slightly diseased persons with healthy kidneys + 5 cases of orthotic albuminuria + 10 patients with slight albuminuria after tonsillectomy etc.). 18 of these 209 determinations gave creatinine clearances of 200 or somewhat more, another 21 cases have clearances of 170—200, but the *average* of the 209 determinations is 135 cm^3 . Loc. cit. p. 260 and following we discussed another 20 cases, 19 of which had healthy or almost healthy kidneys. 2 out of these 19 determinations gave clearances of creatinine between 175 and 200 cm^3 , 17 determinations gave lower clearances, and the *average* of the 19 determinations is 126 . Loc. cit. p. 330 there is a table of 6 creatinine determinations on 1 healthy person, on 1 with diabetes insipidus and on 1 with moderate diabetes mellitus, the clearances vary between 99 and 147, *the average is* 121 cm^3 . Loc. cit. p. 361 shows a further table of 10 creatinine clearance determinations on 10 healthy persons, ranging between the extremes of 85.5 and 144, *average* 112 cm^3 . Loc. cit. p. 383 is a table of 8 creatinine determinations on 8 patients with hypertonia without kidney symptoms in 7 cases, for which latter the *average is* 90 cm^3 . Among the very numerous further creatinine determinations in healthy and diseased kidneys, discussed in the quoted book, there is only a series of 5 determinations on 5 patients with acromegalia, where creatinine clearance *averages* 170 cm^3 , the highest individual figure here being 225 cm^3 . Loc.

cit. p. 451 are 50 determinations on healthy subjects, highest 184, lowest 136, average 158 cc. *The average creatinine clearance of all the above 341 healthy instances is 135.7 cm³.*

As in all series, from which an average is computed, individual determinations vary in both directions from the average. ± 25 to 30 cm³ denotes the extremes of the usual variations, creatinine clearances higher than about 165 and lower than about 100 cm³ being, although by no means exceptional, yet usually not met with. For convenience of calculation I have often used 125 cm³ ± 25 cm³ as an approximate average in my monograph.

The creatinine determinations referred to above have all been executed by kidney workers of undisputable technical skill (Rehberg, Poulsson, Gårdstam, Cambier). Their very great numbers and the close general agreement between them renders it impossible, in absence of other published material than isolated experiments and general references to an unknown number of determinations, to accept Smith's figure of 175 cm³ as a representative average of creatinine clearance in healthy human kidneys.

Quite irrespectively of the question, whether or not the creatinine and inulin clearances really, as a rule, differ so much in man as is stated in individual cases submitted by Smith and co-workers, one thing, however, is obvious from the above. This is, that *the average inulin clearance, submitted by Smith himself and attested by others, does not differ much from the average creatinine clearance* of by far the most extensive series of creatinine determinations yet published, the former amounting to 119—125 cm³, the latter to 135 cm³. One thing more is also obvious, namely, that *the first average (inulin) is well within the range of the most frequent variations comprised in the latter average figure (creatinine).*

If inulin workers base their calculations on an average filtration of 122 ± 20 cm³ per minute, the results of all sound calculations will necessarily be comprised also in the results of all similar calculations based upon creatinine clearances giving filtration volumes of 125—135 cm³ ± 25 —30 cm³. It must be emphasized again, that the two methods do not differ as to the factors to be computed from the filtrate volume or as to the manner of these calculations (cf. p. 117).

Rewording the above discussion, the question whether one experimental method is more accurate or reliable than another cannot possibly arise in cases where the two methods give identical results.

The fact, that the inulin- and creatinine-methods do give identical results in a great number of species, including the common experimental animals, makes thus a heavy inroad upon Smith's rather sweeping statements as to the superiority of the inulin- and the inadequacy of the creatinine-method.

Turning then to such species, where the results of the two methods are said to differ, we find that the difference in results between the two methods is as a rule rather insignificant even in man and apes, where these matters can be best examined. Even in man, where the two methods are said to differ so markedly, the methods agree far more than they disagree. In spite of all Smith's emphasis of great clearance-differences in individual cases, the average inulin clearance as submitted by himself differs but very little from the average creatinine clearance of by far the largest and best-attested series of creatinine tests yet published, and it is in any case well within the range of the ordinary variations of normal creatinine clearance. The consequence of this is, that no otherwise justifiable inference from the results of the creatinine test can possibly disagree with justifiable inferences from inulin tests, and versus.

The great superiority, which Smith and co-workers claim for inulin over creatinine in tests *ad modum Rehbergi*, appears thus rather unwarranted even quite apart from our earlier criticism of their experiments etc.

* * *

This question of superiority is necessarily confined to such species, where the results of the two methods differ; creatinine clearance is always somewhat larger than inulin-clearance in such cases, and this difference must be due to either of the following alternatives, there being no third possibility.

- a) *Either* some creatinine is secreted by the tubules in addition to that which is filtered in the glomeruli,
- b) *or* some of the filtered inulin is reabsorbed from the urine in the tubules.

The arguments, by means of which Smith and co-workers attempt to support the first and to rule out the second alternative, shall not be detailed or scrutinized here, as it is very obvious from the earlier parts of our paper that every one among these arguments is altogether fallacious. Smith's discussion of these alternatives is difficult to follow, as almost every particular line of argumentation is repeatedly broken by excursions into different matters, and as his arguments are not unfrequently derived from evidence that has no or but little bearing on the alternatives discussed. Other arguments, again, are mere analogies drawn from highly conflicting matters. Worst of all, however, is the very incomplete consideration of the experimental results from which Smith's argumentation proceeds. Only certain items of his experiments are taken into consideration; yet the omitted items of the same experiments are in every instance important enough to negative Smith's argumentation.

* * *

The alleged tubular excretion of creatinine, said to occur in man and apes, has thus neither been proved, nor, indeed, been rendered likely at all. There is, further, complete disagreement between this alleged tubular excretion and certain «kinetic» laws and formulas, which Smith and co-workers claim to have substantiated in the case of tubular secretion and resorption, and which they regard as exceedingly important. It is a matter of some consequence, that this serious disagreement occurs in creatinin experiments on anthropoid apes, because among those species, where the clearances of creatinine and inulin differ, apes afford possibilities of adequate analysis of the matter.

* * *

The alleged tubular excretion of creatinine is, further, quite negated by experiments submitted by me from earlier literature. As a matter of fact, a phenomenon, which Smith and his followers regard as a most essential characteristic of every kind of tubular secretion, including alleged tubular secretion of creatinine, is in these experiments shown to occur also in species (rabbits), where according to Smith himself all the urinary creatinine is excreted by means

of glomerular filtration and none by means of tubular secretion. This change in the renal elimination of creatinine is very marked in the rabbits. These rabbit experiments, moreover, give a definite explanation of this phenomenon on lines that have nothing in common with tubular excretion of creatinine.

* * *

Tubular secretion of a part of the urinary creatinine is clearly out of the question in man and apes. Therefore only the second alternative remains for explaining the difference between the creatinine- and inulin-clearances, namely, that a fraction of glomerularly filtered inulin is reabsorbed in the renal tubules of primates. The first conclusion can also be supported by a great number of further facts and calculations, that are outside the scope of this paper and have not been discussed here. The second conclusion receives a strong direct support from the observation, that phloridzin equalises the difference between the inulin- and creatinine-clearances in apes, just as it renders the clearances of glucose and of all other sugars equal to creatinine clearance. In the case of all these sugars this effect is certainly due to phloridzin paralysing the tubular mechanism of sugar resorption, as Smith himself admits. A different interpretation of the same effect in the case of Inulin is altogether unwarranted. It must also be remembered, that inulin is a colloid carbohydrate of starch-like nature. The large size and the general inertness of its molecules may well account for the fact, that inulin is not resorbed by the renal tubules of those species, where inulin-clearance normally equals creatinine-clearance. This however, constitutes no a priori reason against partial resorption of filtered inulin in the tubules of other species, i. e. species with a normally lower inulin- than creatinine-clearance. The fact, that inulin is closely related to that excellently resorbable sugar, fructose, renders such resorption of inulin rather likely in the renal tubules of at least some species.

* * *

Several further questions concerning renal tests *ad modum Rehbergi* will be discussed in a following paper in this journal.

Conclusions.

Inulin and creatinine tests are identical in conception and execution, except in so far that different test-substances are administered. They yield identical results in most animal species including the common experimental animals. The results differ somewhat in man and anthropoid apes, but this is due to partial tubular resorption of filtered inulin, and is absolutely not due to tubular secretion of part of the urinary creatinine, as is alleged by Smith and his co-workers.

The chief interest of the inulin test is *not* due to its giving somewhat different results from Rehberg's test in man and apes, but to its giving *identical* results in most other species. The reliability of Rehberg's test is due to reasons not discussed in this paper. I have regarded it as superfluous to particularize those reasons here, because Smith and his co-workers have not criticized them or taken them into consideration at all, but have instead based their attack on Rehberg only on the alleged superiority of their insulin-test. The reliability of Rehberg's test, however, is not lessened but enhanced by the three facts, *that* identical results are obtained in most species with quite another test substance, inulin, *that* somewhat different results in man and apes certainly are due to other causes than irreliability of the creatinine test, *and that* the information to be derived from these tests is not materially affected by using the one instead of the other test. Regarded from these points of view, Smith's inulin test is an interesting contribution to renal physiology.

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Metabolism of copper in man.

By

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Introduction.

Copper is important in modern medicine for two reasons:

In the first place it is apparent that copper influences many biological processes. It is not only, as Hart and his collaborators found in 1928, indispensable for the formation of hemoglobin in mammals and birds, there also exists a connexion between copper and pigment formation (9, 50, 69.) and between copper and carbohydrate metabolism (2, 32, 52.) and in recent years it has been discovered that copper, as well as iron, plays an important part in tissue respiration; it is even probable that various oxidases are compounds of copper with protein (8, 20, 39, 59).

In the second place the therapeutic significance of copper must be mentioned. Copper as a remedy has been in use for a long time. The Egyptians already 1500 years before the beginning of our era applied copper salts as a medicament and the Greeks in the time of Hippocrates already perscribed copper compounds for pulmonary diseases. In Western medicine Paracelsus introduced copper in the treatment of nerve diseases, lues and affections of the lungs and particularly in the 19th century all sorts of copper compounds came into use in the most widely different diseases. In the 20th century however copper as a remedy began by receding into the background, although, particularly in French medical

literature, it is noted here and there as a remedy for all sorts of infections.

Latterly there appears to be a change on the way. After the experiments of Hart it was natural that copper should again be resorted to as a remedy in the treatment of anemias and the literature on the subject gives the impression that in some cases of anemia, especially in young children, treatment by iron and copper is more effective than by iron alone (29, 55, 57).

Moreover in recent years copper has come into use as a remedy in chronic rheumatism and in tuberculosis. In these cases it is injected intravenously in the form of an organic compound, «*ebesal*». The results in chronic rheumatism are not nearly so good as the first reports on the subject by Fenz led to believe but in various forms of tuberculosis it does actually appear that copper can have a favourable effect and that it increases the resistance to the infection (1, 18, 51).

Up till now most of the investigators who were interested in the rôle of copper in the human organism have concerned themselves with its therapeutic action and toxicology and with the copper content of the blood and organs in normal and diseased subjects. About the absorption and excretion of copper in man, about copper metabolism in a narrower sense, comparatively little had been found out up to the present. That is the reason why we have devoted this study to this subject.

Data on copper metabolism in the literature.

The Absorption of Copper from the Intestines.

In all foodstuffs and also in our drinking water there is always some copper. The estimates of the copper content of foodstuffs vary very much with different authors. This need not depend solely on the different technique used to determine the copper. The copper content of plants for instance varies namely with the richness in copper of the soil in which they are grown and may be therefore twice as high in one case as in another (12). We give here in Table 1. a few figures derived from an exhaustive study by Lindow (36). The copper content of calves liver is strikingly high (44 mg per kg), also of oysters (30.7 mg per kg) and of choeco-

Table 1.

The copper content of various groups of foodstuffs (according to Lindow).

Class of food materials	Copper content. mg per kg (average)
Nuts	11.6
Cereals	4.7
Dried fruits	4.2
Various kinds of fish	2.5
Animal tissues	1.7
Roots, tubers, stalks and bulbs ..	1.4
Leafy vegetables	1.2
Fresh fruits	1.0

late (26.7 mg per kg); strikingly low that of pure unpasteurized cows milk (0.14—0.20 mg per liter) (34). The copper content of human milk is about three times as high (70).

It is not known if man can dissolve and absorb in the intestines the copper equally well from all these organic substances. In experiments on anemic rats the absorption of copper from organic compounds appeared in any case to take place just as well as from inorganic salts; only the insoluble copper sulfide and copper porphyrin were absorbed little if at all (56).

With a normal diet it may be assumed that an adult ingests about two to three mg of copper with his food per day and excretes it again in urine and faeces. This appeared in the balance studies of Tompsett and it corresponds with the figures of Chou and Adolph whose experiments for the rest did not last long enough in our opinion to permit further conclusions to be drawn.

It is not yet exactly known how large the percentage of copper is that test animals or man can absorb via the intestinal wall into the body from foodstuffs or supplementary copper salts. Balance studies have however been done on animals and human beings which determine how much copper was administered with the food in a definite length of time, how much was again excreted with the urine and faeces and how much was retained in the body. The copper that was recovered in the urine and the quantity that was deposited in the tissues was then in any case absorbed through the wall of the intestines.

It is probable however that still a third fraction was absorbed which in these experiments had escaped observation. It has namely been ascertained that copper can again be excreted together with bile into the digestive tract and, as we shall see later, it is also quite possible that copper is not only absorbed through the intestinal wall but can also be excreted. We probably recover in the faeces copper that has made this circuit and it is not possible to tell by means of ordinary experiments how large this last fraction is in the excreta and which portion of the copper in the faeces has passed through the intestinal tract without being absorbed and excreted again.

Probably therefore the figures which we find in literature for the percentage of copper which can be absorbed are on the low side.

In order to get an idea of the absorption of copper out of normal food by test animals we have borrowed a few figures from the experiments of Lindow, Peterson and Steenboek. On an average in the faeces of two rats about 30 % of the ingested copper was not recovered; by far the greater portion of this copper appeared in the urine. It must be noted however that Sandberg and others found the copper content of the urine of a rat to be much lower (48). In rabbits Sandberg and Holly have ascertained that 30 % of the copper in the food is excreted in the urine. The results of experiments on human beings correspond very well with the results of these tests on animals. Thus Seoular who did balance studies on children from three to six years found that no less than 42 to 85 % of the copper that was present in the foodstuffs was absorbed in the intestines and far the greater part of it was deposited in the body. Only 2 to 6 % was eliminated in the urine. Daniels who made similar investigations with children of the same ages arrived at figures of the same order.

In any event from these data the conclusion may be drawn that the animal and human organism is capable of dissolving and absorbing a large part of the copper in normal foodstuffs.

When extra copper in the form of copper salts is administered per os, experiments show that a clearly observable quantity of this also is absorbed by the body. Flinn and Inouye who gave, in the course of 82 days, 1203.5 mg of copper, dissolved in the form of copper chloride in drinking water, recovered 11.34

mg of copper in the bodies of the rats and 12.36 mg in the urine. They neglect the quantity of copper which is normally present in the bodies and urine of rats.

A higher percentage of the copper is absorbed if it is given for a shorter period. In Lindows balance studies a rat that got 30 mg extra copper every six days, retained in its body 18.5 % of the copper administered in the first period and in the second period of six days 10 % of the extra copper; in the third period there was already more copper excreted in the urine and faeces than was ingested in that time. Filehne found in a rabbit that had received a very large quantity (the half of the lethal dose) of sodium copper-tartrate all at once by mouth, and had been killed 36 hours later, that 25 % of the copper could not be recovered from the contents of the intestines and in the faeces and therefore must have been absorbed into the body. (15).

We did not find in the literature available here at present any mention of tests on human beings for the absorption of copper salts.

The Distribution of Absorbed Copper in the Organs.

It might be expected that, after the administration of a soluble copper salt which as we have seen is in part absorbed by the body, a temporary rise in the copper content of the blood could be demonstrated. This only succeeds when a very large dose is given. Thus Eden and Green found that in sheep the copper content of the blood only rises if more than 2 g of copper sulfate is introduced all at once into the stomach with a stomach tube. With still larger doses in their tests the copper content of the blood rose to 6 to 8 times the initial amount. Flinn and Inouye found in dogs who received no less than 500 mg of finely pulverized metallic copper per day a copper content of 2.97 mg % in the plasma and 1.27 mg % in the red blood corpuscles, amounts respectively 20 and 10 times as high as the normal content.

The tests of Schürhoff, also on sheep, who thought he could demonstrate a rise in the copper content of the blood after the administration of copper salts by mouth are not in our opinion entirely convincing. From his data namely it is not possible to make perfectly sure if the variations which he observed in the

copper content after the dose of copper were greater than the variations which might be expected in the results obtained by the technique of copper determination used by him.

The only investigator who describes an increase in the copper content of the blood (the serum in this case) after only a small dose of copper salt is Sachs (47). Unfortunately only a summary of his article was obtainable. Guillemet, who gave a somewhat larger dose to the same test animal, a dog, found no subsequent rise in the copper content of the blood or of the serum. Probably the absence of a rise after the administration of a small dose must be because the copper that is absorbed into the blood of the vena porta is immediately deposited in the liver.

The *liver* namely is the organ in which the largest portion of the copper which is assimilated through the intestines or administered intravenously is stored. In rabbits (27, 41) as well as in rats (27, 33) the copper content of the liver can rise to an amount 50 to 100 times as great as that in normal test animals when for several months large quantities of copper salts are administered per mouth. In the other organs under these circumstances copper is either not stored at all or is stored in much smaller measure. In the kidneys the copper content of the rat can rise to double the amount (33, 37); the different investigators do not agree about the possibility of a deposit of copper in the spleen (3, 27, 33, 37).

If a large, just short of deadly dose of soluble copper salt is injected intravenously into rabbits or sheep the largest part will at first be recovered in the plasma. Within a few hours the distribution between the plasma and the blood corpuscles has become even. The copper content of the blood as a matter of fact sinks rapidly after the injection to the normal amount: in 6 to 24 hours the normal height of the copper content is reached again (11).

The Excretion of Copper with the Urine.

In all test animals and also in man, copper as a rule is found in the urine. Opinions however differ widely as to the normal content. We shall limit ourselves here to the statements which refer to man.

Rabinowitch found in *adults* amounts which vary from traces to 0.7 mg per day, Tompsett gives 0.12 to 0.52 mg as a normal amount and Heilmeyer speaks of «at most the merest traces». According to Tompsett the variations from day to day in the same person are as great as the differences in the excretion of different people. The copper content in the urine of *children* is about equal to that of adults; the total quantity which they excrete per day is proportionately lower (10, 28, 45). With test animals the copper content of the urine increases as a rule when extra copper is given *by mouth*. The quantity excreted through the kidneys remains small however compared with the quantity ingested. Flinn and collaborators in his balance studies on rats recovered about 1 % of the copper taken by mouth and from the figures of Lindow and coll. it appears that with their rats at most 1.7 % of the extra copper given was recovered in the urine. At the same time the copper content of the urine had risen to about 5 times the normal amount. Brandl reports that he also observed in a dog a copper excretion through the kidneys after administration by mouth of a copper salt. Filehne is the only one who can point out in the urine a large portion (more than 25 %) of the copper salts which he had given by mouth to test animals. The dose which he gave to his rabbits was so strong that it was immediately followed by a complete anuria lasting 36 hours!

In man, Lehman in 1891 already, found that of 30 mg copper that he gave per os not less than 4 to 5 mg were excreted in the urine in three days. It is however a question whether the technique of his copper determination was entirely reliable. Hess and Rabinowitch however also both found that in man the copper content of the urine was higher with food rich in copper than with a diet containing less copper.

After *intravenous administration* of a very strong dose of copper Brandl in a dog and Callegari in a rabbit found a considerable copper excretion in the urine. It is known however that with such a high dosage as they used the kidneys of test animals may be harmed. Therefore in our opinion no conclusion may be drawn from these experiments with the regard to the excretion of copper under normal conditions.

Excretion of Copper with the Bile and via the Intestinal Wall.

Brandl found by his experiments on dogs that he had given copper salts by mouth or by injection, a very high copper content of the bile (24 to 350 mg per liter). He does not however give any figures for the normal level of the copper content of the bile and from his description of the technique used for copper determination it cannot be determined with certainty if this may not have depended on a technical error.

Flinn and Inouye saw in a cat that had a fistula on the gall bladder that the copper excretion in the bile, after administration of copper chloride by mouth rose from 0.24 mg to 1 mg per day.

Goralewski, who injected in rabbits intravenously an organic copper compound recovered subsequently an important quantity of copper in the faeces, but he found that the copper content of the bile after the injection had not risen. Uycda and Sugihara also think that no distinct excretion of copper takes place with the bile.

These data out of the literature differ widely and do not permit any further conclusions to be drawn.

There is still only very little known about copper excretion with the bile *in man*. It had early already struck a few investigators that gallstones except purely cholesterine stones contained a comparatively large amount of copper (53, 54). Systematic investigation of the excretion of copper with the bile have up till now scarcely been performed. A few data were found in an article by Judd and Dry, who determined the copper content of 19 gall bladders of surgical cases and in the bile emanating from a hepaticus drain in three other victims of gall bladder complaints, who had been operated. The copper content varied in the first group from 0.091 to 1.07 mg per 100 cm³ and in the second group from 0.063 to 0.325 mg per 100 cm³. It goes without saying these figures cannot be compared without question with the amounts which are found in healthy people.

From the tables of Lindow and collaborators (37) it appears that in the rat a distinct excretion of copper takes place in the intestines either with the bile or through the intestinal wall. The test animals were first of all given during 18 days copper sulphate by mouth. When subsequently during 6 days the extra copper

dosage was stopped the copper content of the excreta still remained during 6 to 12 days distinctly higher than in the control period which preceded the administration of the copper. After six weeks the copper content of the faeces and urine had not only become normal again but it appeared that the copper content of the liver had also sunk to normal.

Goralewski, Calligari and Sugihara also found in the rabbit an increased copper content of the contents of the bowels after an intravenous administration of copper. They assumed an excretion of copper through the intestinal wall. For the sake of completeness we shall still mention here the tests of Sandberg and collaborators which seem to indicate that perhaps the spleen also plays a part in the metabolism of copper. He found namely in rats as well as in rabbits that the removal of the spleen causes a rise in the excretion of copper in the faeces. (48, 49).

We could not find in medical literature any data on copper excretion with the bile or via the intestinal wall in man after administration of copper by mouth or by intravenous injection of copper compounds.

Present Investigation.

A. Technique of Copper Determination.

Since Sarzeau in 1832 as a pioneer performed the first quantitative copper determinations in organic material (13), dozens of different methods have been worked out. It is outside the scope of this study to discuss them. They are described for a large part in the exhaustive review by Heilmeyer (25).

We chose the carbamate reaction which was first used by Délépine (67) and later was reintroduced by Callan and Henderson (5). This method is not complicated but withal so sensitive that by it the small quantities of copper occurring in a few cubic centimeters of blood or bile can be exactly determined.

The principle of copper determination with sodium diethyldithiocarbamate.

When cupric ions are combined with a solution of sodium diethyldithiocarbamate in water a golden yellow copper carbamate compound arises which can be extracted with amyl alcohol (40), and of which the colour intensity is in proportion to the copper content, independent of the pH of the milieu and the concentration of the reagent. This reaction is not

entirely specific. Particularly iron can easily cause disturbances since it gives with carbamate a brownish yellow colour. For this reason sodium pyrophosphate is added to the liquid to be examined, which in an alkaline medium forms a non-ionised compound with the ferric ions so that the reaction of the carbamate reagent with the cupric ions cannot be influenced.

Cobalt can form with the carbamate a yellow compound. By the addition of sufficient ammonia it is not necessary to expect any inconvenience from this because the intensity of the colour of this compound is much weaker than that of copper carbamate and the concentration of cobalt in the materials examined by us lies deeper than that of the copper. (31, 62). Lead, zinc, manganese and a number of other rarer metals can if they are present in comparatively large quantities cause a clouding with the reagent. We did not experience from this any inconvenience in our determinations.

Copper Determination in Blood, Bile, Gastric Juice, Faeces and Urine.

Chemicals: We used sodium pyrophosphate, sodium diethyldithiocarbamate, 30 % hydrogen peroxyde, 25 % ammonia and 25 % hydrochloric acid of the Merck Company, and sulphuric acid (S. G. 1.84) according to the Netherlands pharmacopoea.

The trichloroacetic acid and the concentrated nitric acid were distilled before use in a glass apparatus; the same was done to the amyl alcohol used, which had previously been dried with calcium chloride.

For making the solutions, diluting of serum etc. redistilled water was always used.

Filters: We always used the ironfree filters of Schleier and Schüll, No. 589², 9 cm in diameter.

Glassware: It appeared to us that for the cleaning of separators, pipettes, test tubes, etc. it is sufficient to thoroughly rinse them with the tapwater in our laboratory which contained about 0.100 mg Cu. per liter. After cleaning, the glassware was as far as necessary dried in an oven, only the porcelain bowls in which the faeces were dried, had to be treated for several hours with a mixture of 50 cm³ nitric acid and 1 liter of concentrated sulphuric acid, before they were cleaned with water.

By blank determinations we convinced ourselves that the glassware, the puncture needles of rustless steel, the receptacles for faeces and urine, the duodenal tubes and such did not contain any disturbing amount of copper.

Determination of Copper in Serum and Blood.

We followed on broad lines the method of Heilmeyer (25), which we had to revise however as we did not dispose of any micro-cups with the photometer and in any case did not wish to use more than 6 cm³ of blood or serum per analysis. Furthermore we took a weaker carbamate solution, such as Miss Steussy (62) has reported. We could confirm her favourable results.

6 cm³ of blood made non-coagulating by copper free liquid (Roche) or 6 cm³ of serum which is obtained by collecting the blood in a centrifuge tube and after clotting, for 10 minutes centrifuging it, is pipetted in a large centrifuge tube of 50 cm³. To this is added 18 cm³ of aqua bidest. (from a burette) and 6 cm³ of 20 % trichloroacetic acid. Mix thoroughly with a stirring stick, wait ten minutes, then centrifuge for ten minutes (3000 turns per minute).

After the protein has been precipitated in this way and the copper has been released by the acid, 20 cm³ of the supernatant liquid is pipetted in a separator of 75 cm³. To this are added 4 cm³ of 4 % sodium pyrophosphate, 2 cm³ of 25 % ammonia, 5 cm³ of amyl alcohol and 0.5 cm³ of 1 % sodium diethyldithiocarbamate and shaken vigorously for one minute. The separator is allowed to stand until the upper alcohol layer has entirely separated itself from the liquid below; this is slowly drained off and the amylalcohol is poured through a filter, which retains the still present water, into a test tube. Once in a while the amyl alcohol remains cloudy after pouring off. By centrifuging this emulsion and then letting the water run off in a separator before filtering, it is usually possible in these cases also to eliminate the water from the amylalcohol.

The intensity of the yellow colour of the amylalcohol is measured within the hour in a «Pulfrich Stufenphotometer» in a 10 mm cup, with the filter S—13. The quantity of copper expressed in micro grams (μ), is then 26 times the recorded extinction. Since only 20 cm³ of the 30 cm³ (blood + water + trichloroacetic acid) is used for the actual determination the quantity of copper that is found derives from $20/30$ of 6 cm³ = 4 cm³ of blood (serum). In order to find the copper content per 100 cm³ of blood or serum it is necessary merely to multiply the amount recovered by 25.

In spite of all precautions some traces of copper are released from the chemicals and the glassware used in every assay so that the amount recovered is too high. Therefore is always necessary alongside the actual copper determination to perform a blank determination, which is done exactly as the other analysis except that in place of 6 cm³ of blood or serum 6 cm³ of redistilled water are used. The result of this «blank» is then deducted from the result of the actual test.

Determination of Copper in Bile and Gastric Juice.

Since in the determination of copper in the bile the extraction of the copper with trichloroacetic acid did not give satisfactory results the organic material was first destructed with sulphuric acid, nitric acid and 30% hydrogen peroxide.

To 4 cm³ of bile or gastric juice are added in a pyrex destruction tube a few pieces of quartz to prevent bumping, 2 cm³ of concentrated sulphuric acid and 3 cm³ of nitric acid after which the liquid is carefully heated over a flame until the mixture has turned black and white clouds have been developing in it for several minutes. It is then cooled for about one

minute, thereupon $2\frac{1}{2}$ cm³ of 30 % hydrogen peroxyde are added to it drop by drop, after which the liquid is again heated until white clouds form. This process if necessary may be repeated once or twice with for instance 1 cm³ of hydrogen peroxyde, until a crystal clear solution has been obtained. This is decanted into a separator, the tube is rinsed three times with in total 25 cm³ of redistilled water; 4 cm³ of sodium pyrophosphate are added, the liquid is made alkaline with ammonia, is cooled, and the determination subsequently carried out in the same way as described for blood.

Alongside it a blank determination is always performed with the same chemicals without bile or gastric juice.

Determination of Copper in the Faeces.

The faeces are placed in a previously weighed porcelain vessel and dried for about 12 hours in an oven at a temperature of fully 100° or on an asbestos plate over a flame. Afterwards the dish with the dry faeces is weighed and the latter is transferred with the help of a porcelain spatula to a mortar and pulverized. A sample of the powder of 400—500 mg is carefully weighed off. This is put into a destruction flask of 300 cm³ with a few pieces of quartz and 6 cm³ of concentrated sulphuric acid and heated violently for a few minutes. After cooling 20 cm³ of perchloric acid are added and the mixture is evaporated for about 30 minutes until a fairly colourless, slightly cloudy liquid remains. When the contents of the vessel have cooled again, $2\frac{1}{2}$ cm³ of hydrochloric acid and about 50 cm³ of redistilled water are added to it; the liquid is poured off through a filter into a 100 cm³ volumetric flask. The Kjeldahl flask and filter are rinsed three times with about 15 cm³ of redistilled water and the volumetric flask filled up to 100 cm³. Of this 20 cm³ are taken (or, if the faeces are very rich in copper, 5 cm³) and the copper content of it is determined as described for the bile. This assay is also accompanied by a blank.

A simple calculation gives the copper content of the sample of faeces that was dried.

N. B. With this method of destruction it is well to be on guard against the explosive properties of perchloric acid.

Determination of Copper in the Urine.

40 cm³ of urine with 4 cm³ of concentrated sulphuric acid, 5 cm³ of nitric acid and a few pieces of quartz are evaporated in a 300 cm³ destruction flask to a black mass. To this is added, as described for the bile, hydrogen peroxyde, and when a crystal clear liquid has been obtained the contents of the retort are rinsed out into a separator. Before the addition of ammonia in this case, besides 4 cm³ of sodium pyrophosphate, 1 cm³ of 20% sodium citrate is added in order not to be inconvenienced by the formation of insoluble calcium phosphate (65). This estimation is also accompanied by a blank.

Accuracy of the Method.

In order to investigate the reliability of our method we performed first of all a series of determinations with a known quantity of copper. For this we used three different standard solutions of copper sulphate, acetized with a little hydrochloric acid to prevent the absorption of copper by the glass surface and pipetted it off in carefully measured quantities.

We performed 5 analyses with a quantity of 2 γ, 5 with 4 γ, 3 with 10 γ, 1 with 20 γ and 3 with 20.87 γ of copper. In this range there is a constant relationship between the extinction coefficient and the concentration of the copper, the light absorption obeys the Lambert-Beer law. In our analyses the extinction coefficient, in using 5 cm³ of amylalcohol and filter S 43 appeared to amount to 0.0385 per g of copper. It is thus possible to find the number of micro grams of copper in the sample examined by multiplying the extinction coefficient read, by $1/0.0385 = 26$. It appears that the maximum error in determinations with 2 γ was 15 %, with 4 γ 7 % and with more than 4 γ 4 %.

The accuracy of the determination in blood and serum was tested first of all by doing 6 analyses in duplicate and 3 analyses in triplicate. The greatest difference between two analyses on the same sample amounted to 10 %. Furthermore we added to three samples of serum of which the copper content had previously been determined, 8 γ of copper and did the determinations over again. The additional copper was recovered with a maximum error of 7.5 %.

Finally we determined the copper content of three samples of serum and three samples of blood side by side, after treatment with trichloroacetic acid and destruction as described for bile. It appeared that the differences came within the above mentioned margin of error so that it may be assumed as indeed it is stated in literature (25) that with trichloroacetic acid all the copper in blood and serum is released.

In order to discover the margin of error in our determination of copper in urine, bile and faeces we added to a few samples of which the copper content had previously been determined, a known quantity of copper and then tried to find out in a second test if the additional copper could be recovered with sufficient accuracy. 8 γ of copper added to 4 different samples of urine were recovered with a maximum error of 10 %. 8 γ of copper added to 2 different samples of bile were recovered with a maximum error of 7.5 % and 41.75 γ of copper in 4 samples of faeces were recovered with a maximum error of 10 %.

The results of the blank determinations were fairly constant. In the blank tests in blood, serum, gastric juice, bile and urine we found 0.5—0.87 γ of copper per determination, in faeces 4.25—6.5 γ. It is permissible to conclude from these data that the method described is sufficiently accurate for our purpose. In the determinations of blood, bile and faeces the error in an analysis may be estimated at atmost 10 %; in urine and gastric juice where the copper content is sometimes very low the error in determination is naturally proportionately higher.

B. Copper Metabolism in Man.

In our own investigations we have tried to find out to what extent man absorbs a copper salt, administered by mouth and subsequently how the excretion of the absorbed copper takes place and particularly if the copper content of the bile increases after administration of copper.

We furthermore investigated the excretion via urine, bile and faeces of copper, injected intravenously after we had first examined how quickly the administered copper disappears out of the bloodstream.

Copper content of bile, gastric juice and urine in normal persons.

Before we describe our further tests we must first discuss the normal levels of the copper content of bile, gastric juice and urine in our test persons.

In Table 2 are data which we collected about 8 normal persons whose bile we obtained once or twice with a duodenal tube of

Table 2.

The copper content of the bile and gastric juice in normal subjects ($\gamma\%$).

Nr	Subject	Bile	Gastric Juice
1.	Female aged 30	35	15
2.	Male aged 30	60	35
3.	Female aged 25	{ 75 80	10
4.	Female aged 23		40
5.	Female aged 25	115	25
6.	Female aged 30	{ 120 135	10
7.	Male aged 33		25
8.	Female aged 35	205	

Table 3.
The copper content of the urine in normal subjects.

Day	Female, aged 23		Male, aged 30		Male, aged 40		Male aged 23	
	Copper content (γ %)	Copper per day (γ)	Copper content (γ %)	Copper per day (γ)	Copper content (γ %)	Copper per day (γ)	Copper content (γ %)	Copper per day (γ)
1	4.5	20	2	25	3.5	45	3.5	55
2	12.5	100	6	70	2	35	2.5	35
3	5.5	45	6	60	0	0	2.5	40
4	5	30	6.5	65	0	0	trace	trace
5	5	50	2	15	4	30	trace	trace
6	4	15	3	55	—	—	trace	trace
Average	6	43	4.25	48	2	22	1.4	22

Einhorn. The copper content of the bile («A-bile») amounted to from 35 to 205 γ %. The copper content of the gastric juice was always lower than that of the bile and amounted to from 10 to 40 γ %.

In order to discover the normal copper content of the urine we determined the copper content in the urine of 4 normal persons and the total quantity excreted in the urine, during 5 or 6 days. During this period the diet was not altered. As may be seen in Table 3 the levels vary widely but they are in any case very low, compared to the copper content of bile and faeces. We found in the urine a content of 0 to 12.5 γ % and a total quantity per day of 0 to 100 γ copper, while the average excretion per day varied from 22 to 48 γ . These figures are lower than generally found in medical literature, only Heilmeyer also says that he found at most traces of copper in the urine, without giving any figures. Tompsett and Babinowitch who performed this test on a much larger series of adults found alongside of equally low figures also levels of 41 and 48 γ %. It is possible that this difference is due to an error in their technique or in ours; it is also quite conceivable that if we had examined an equally large series of persons we might have found among them equally high levels.

Absorption and excretion of copper after administration by mouth.

In order to trace the absorption and excretion of the copper we went to work as follows:

For three test persons in whom a clinical examination had not found any abnormalities, a diet was prescribed that during the whole test, i. e. for at least 21 days, consisted each day of the same solid and liquid food in the same quantities. Care was taken that they should entirely consume this ration and not eat anything on the side. In order to make the test more or less attractive the diet was previously discussed with the test persons and prepared as far as possible in pre-war style. After they had taken this ration for at least 3 days all urine and stools were collected in 24 hour portions. For the analysis of the faeces we usually took 3 daily portions at once.

Now during a control period of 6 days the copper excretion in faeces and urine was determined, besides which the copper content of the bile in test persons A. and B. was estimated. In this way an impression was gained of the normal (basal) excretion of copper of the test person with this particular diet. Hereupon he received in the course of 3 days 9 cachets with 50 mg of copper sulphate with his meals. To the first and last dose a half gram of carmine was added in order to mark the feces belonging to it. By comparing the copper content of the faeces in this second period with that in the control period preceding it we could determine what portion of the copper sulphate was excreted directly in the stools and how much copper remained in the body. Considering that in the intestines not only an absorption but also an excretion of the copper can take place it is naturally quite possible that already in this second period a part of the copper, that had been absorbed by the intestinal wall, was excreted again into the intestines. In this case the percentage of the dose of copper that is absorbed is still higher than we were able to demonstrate with this arrangement of the experiment.

After all the carmine in the faeces had disappeared and we might assume that also the copper sulphate which was mixed with the food had been eliminated from the intestines we again determined for a period of 6 days the excretion of copper in the urine and faeces and compared this with the excretion of copper during

Table 4.

Absorption and excretion of copper after administration of copper sulphate by mouth. Test subject A (female, aged 23).

Day	Copper content of the bile	Copper content of the urine		Copper content of the faeces	Notes
		γ per day	Average	Average per day	
1		20			Control period (normal excretion).
2		100			
3		45	43 γ	3.28 mg	
4		30			
5		50			
6	85 γ %	15			
7		35			All together during this period: 114.56 mg. Cu extra were administered, 82.04 mg. Cu extra were excreted. 32.52 mg. Cu were retained in the body.
8		25			
9		35	41 γ	13.67 mg	
10		30			
11	235 γ %	60			
12		60			
13		60	45 γ	5.23 mg	1.95 mg Cu extra excreted per day.
14		30			

the control period in order to see if part of the absorbed copper was again eliminated from the body by this route. In test persons B. the copper content of the bile was again determined in this period.

Notes on test subject A.

In Table 4 the results of our first experiment are collected. After the normal copper excretion with a regular diet had been determined during 6 days (43 γ copper per day in the urine and 3.26 mg per day in the faeces), the test person was given during the first 3 days of the second period 50 mg extra of copper sulphate three times a day (in total 114.56 mg of copper). After this treatment the excretion of copper in the urine remained the same, in the corresponding faeces in this period of 6 days a total of 82.04

Table 5.

Absorption and excretion of copper after administration of copper sulphate by mouth: Test subject B (male, aged 30).

Day	Copper content of the bile	Copper content of the urine		Copper content of the faeces	Notes
		γ per day	Average	Average per day	
1		25			
2		70			
3		60	48 γ	2.10 mg	Control period (normal excretion).
4	60 γ %	65			
5		15			
6		55			
7		15			All together during this period: 114.56 mg. Cu extra were administered, 83.07 mg. Cu extra were excreted, 31.94 mg. Cu were retained in the body.
8		trace			
9	90 γ %	trace	24 γ	15.94 mg	
10		35			
11		50			
12		35			
13	317 γ %	75			Per day during this period: 1.72 mg. Cu extra were excreted 0.67 mg. Cu extra were administered.
14		trace			
15		trace	17 γ	3.82 mg	
16		0			
17	210 γ %	15			
18		15			
19	195 γ %				

mg more copper were excreted than in the previous period. Thus $114.56 - 82.04 = 32.52$ mg of copper or 29 % of the copper sulphate given, were retained in the body.

The third period was terminated too soon and was therefore too short to permit of definite conclusions. It may be said however that the impression was gained that the copper content of the faeces had risen and that thus a part of the absorbed copper was probably excreted again via the stools.

The copper content of the bile is noticeably higher after the administration of copper than before.

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Table 6.

Absorption and excretion of copper after administration of copper sulphate by mouth. Test subject C (female, aged 26).

Day	Copper content of the <i>urine</i>	Copper content of the <i>faeces</i>	Notes
	Average per day	Average per day	
1 till 6	14 γ	1.42 mg	Control period (normal excretion).
7 till 15	18 γ	9.62 mg	All together during this period: 114.56 mg. Cu extra were administered, 86.62 mg. Cu extra were excreted, 27.94 mg. Cu were retained in the body.
16 till 21	16 γ	3.35 mg	Per day during this period: 1.93 mg. Cu extra were excreted per day.

copper excretion in those 9 days and there were thus 114.5—86.62 = 27.94 mg of copper retained, i. e. 24 %. We were obliged to make in this case the second period rather long, 9 days, in order to be certain that at the end of it all the copper sulphate out of the food had disappeared with the faeces. The copper excretion with the urine rose slightly, the difference with the previous period is however in our opinion of no significance.

During the third period the copper excretion in the stools remained 1.93 mg per day higher than in the control period. Thus here also it seems probable that in that time a part and even an important part of the absorbed copper was excreted again via the intestines. The copper excretion via the kidneys had here also not increased noticeably.

The Excretion of Copper with the Bile.

We examined the excretion of copper in the bile, after administration of copper sulphate by mouth not only in test persons A and B but also in a patient with a light case of bronchial asthma

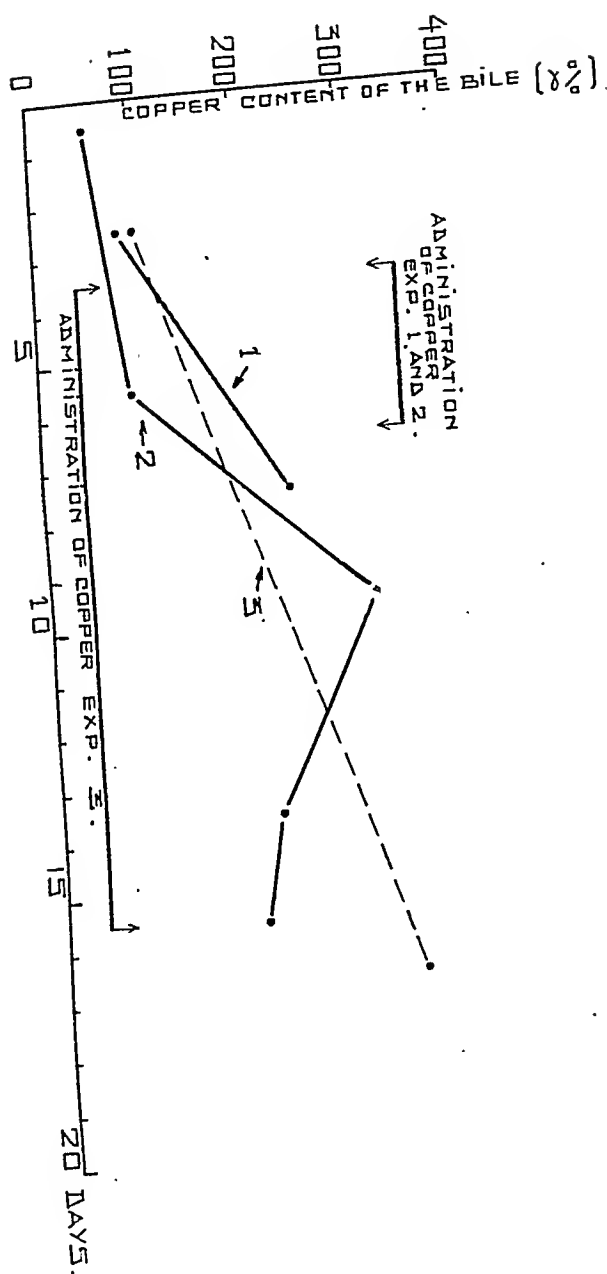


Fig. 1. Copper content of the bile, collected by duodenal drainage, before and after administration of copper sulphate by mouth (150 mg per day).

who was given 150 mg of copper sulphate per day for 14 days. In Figure 1 the data of the three experiments have once more been summed up. It appears that in all three cases the copper content of the bile shows a strong increase. When we examined the bile on the first day after the administration of copper sulphate had been stopped we always determined at the same time the copper content of the gastric juice to see if no more copper sulphate had remained behind in the upper part of the digestive tract. This appeared not to have been the case.

Moreover we investigated the copper excretion with the bile in six surgical cases in whom after a cholecystectomy a hepaticus drain had been applied. As it was possible with them to collect

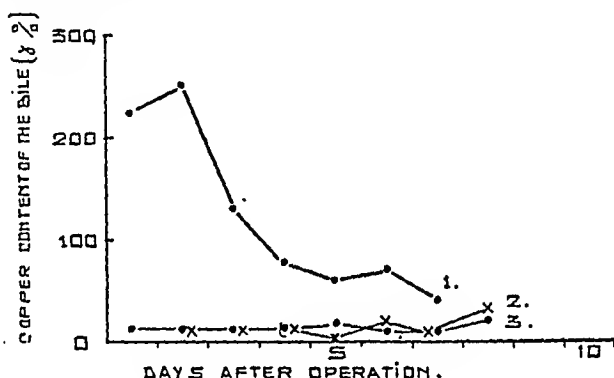


Fig. 2 Copper content of the bile, collected by hepaticus drainage

and examine the bile continuously for many days we were able with these test persons to determine more easily at what moment the increased copper excretion begins to appear after the administration of copper sulphate. Furthermore there is the advantage that the bile collected in this way is not polluted by gastric juice or intestinal juice and also can not be mixed with more or less concentrated bile from the gall-bladder. One great objection to this method consists of the fact that only patients can be examined who shortly before have undergone a serious operation under narcosis and besides that in these people generally a large part of the bile has not reached the intestinal tube so that among other things also a certain quantity of copper in the bile which otherwise might have been absorbed again from the intestinal tract

METABOLISM OF COPPER IN MAN

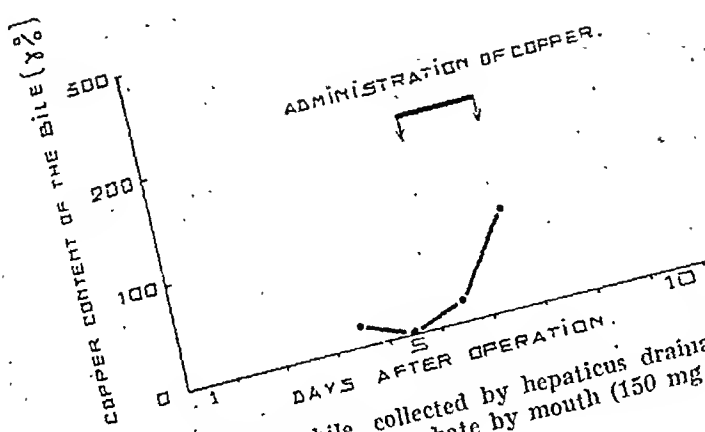


Fig. 3. Copper content of the bile, collected by hepatic drainage, before and after administration of copper sulphate by mouth (150 mg per day).

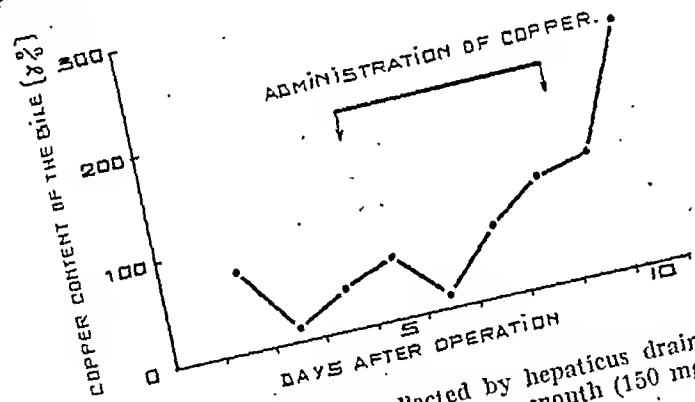


Fig. 4. Copper content of the bile, collected by hepatic drainage, before and after administration of copper sulphate by mouth (150 mg per day).

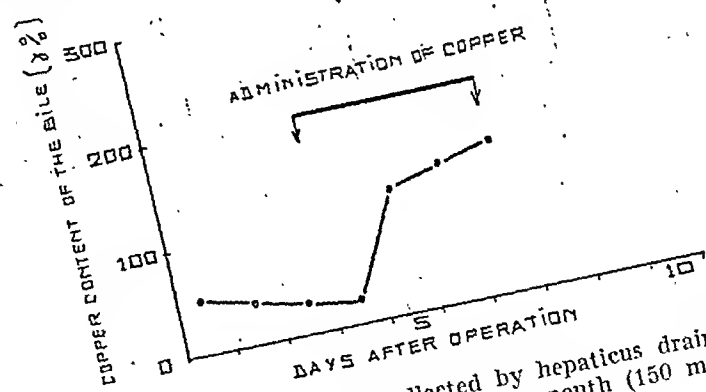


Fig. 5. Copper content of the bile, collected by hepatic drainage, before and after administration of copper sulphate by mouth (150 mg per day).

is in this way withdrawn from the body. Besides these patients in the first week after operation ingest only very little copper with their diet. To this we ascribe the fact that the copper content of the bile in our surgical patients is in most cases so much lower than in normal test persons.

We examined in the first place the copper content of the bile in 3 patients without any extra copper having been given in order to learn the normal variations of the copper content under these circumstances and gave to 3 other patients during 2 to 4 days 150 mg of copper sulphate per day after the bile had already been examined for several days. As may be seen in Figure 2 the copper content of the bile in the first three patients did not show any tendency to rise in the first week after the operation. From Figure 3, 4 and 5, it appears that after administration of copper sulphate the copper content of the bile does in each case show a definite increase; this rise appears only after from 1 to 4 days and reaches its maximum probably still later.

Copper Content of the Blood after Administration of Copper per Mouth.

Finally we investigated whether the absorption of copper after the taking of copper sulphate also promotes a rise in the copper content of the blood or serum by giving to 3 test persons 200 mg of copper sulphate in pills at breakfast and measuring the copper

Table 7.

The copper content of the blood before and after the administration of 200 mg of copper sulphate by mouth (γ %).

Subject.	Time:	0	$\frac{1}{2}$	1	2	4	8	24	hours.
Male. Aged 38	Copper content of the blood	140		150	145	145			
Male. Aged 32	Copper content of the blood	142	130	122	113	137	97	117	
Male. Aged 45	Copper content of the blood	95		112	105	107		105	
	of the serum	98		97	97	105		105	

content of the blood at several different points of time before and after. As may be seen in Table 7 a rise cannot be observed: the variations in the copper content are not greater than normal variations. To a fourth test person, a normal man, we gave during 3 days 150 mg of copper sulphate per day. This also had no influence on the copper level of the blood. As we have already mentioned in the discussion of the literature on the subject, the probability is that the copper after absorption from the intestinal tract and assimilation in the vena porta is immediately deposited in the liver unless a very large dose is given.

Copper metabolism after intravenous administration of copper.

After we had examined the absorption and excretion of copper after administration per mouth it seemed worthwhile to investigate how the body deals with copper that has been injected intravenously, all the more since this method of administration is again in recent years used more frequently in therapy. For this we took

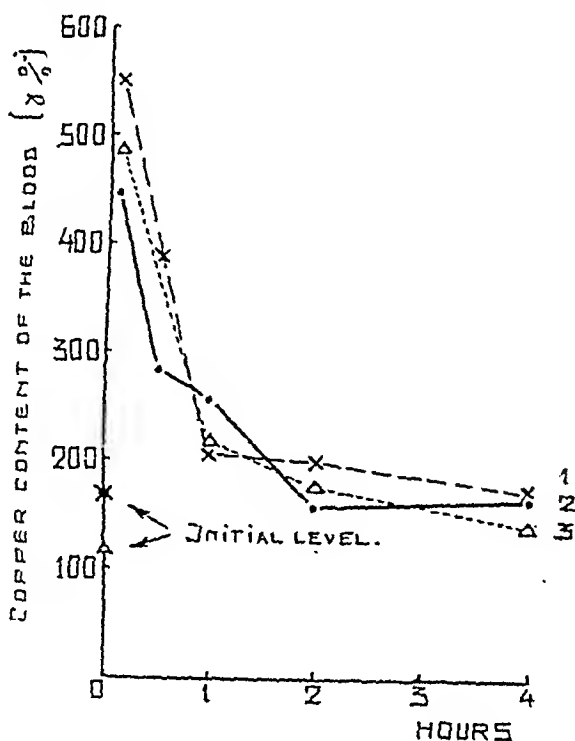


Fig. 6. Copper content of the blood, before and after intravenous administration of copper (100 mg chesal).

a copper compound which latterly has been most used for this purpose and that even in a rather large dose does not have a toxic effect: it is Ebesal of the Bayer Company, an organic copper salt, soluble in water (sodium copperallylthiourea benzoate), that contains about 19 % copper. It is naturally quite possible that the results obtained with this compound do not exactly hold good with anorganic copper salts.

In the first place we investigated how rapidly copper, injected in this way, disappears again out of the blood stream. After we had first for a few days previously given one or two small doses of ebesal as a test dose, we slowly injected intravenously 100 mg of ebesal (19 mg of copper) and measured just before and at several points of time afterwards the copper content of the blood that we drew from a vein in the other arm. The result is to be seen in Figure 6. The copper content of the blood rises right after the injection to three to four times the initial level, and after 2 to 4 hours the copper content of the blood has already become normal again (in test person no. 3 it was after that time still a little higher than the initial level but just about as high as it had been a few days before, when it amounted to 137 γ %). So this agrees with the data collected with the test animals.

Copper Excretion with the Bile, Urine and Faeces.

In order to determine the excretion of copper after intravenous injection we proceeded in the same manner as for the experiments for which copper sulphate was given by mouth. The two test persons, both healthy men, first were given for three days a regular diet, whereupon the excretion of copper with that diet was determined for six days. After that they received three intravenous injections of ebesal while the copper excretion via bile, urine and faeces in that period and at least six days following was checked over again. The diet in this case also remained the same throughout the entire experiment.

Notes on test subject D.

During the control period the average excretion of copper per day amounted to 22 γ with the urine, and with the faeces 2.33 mg.

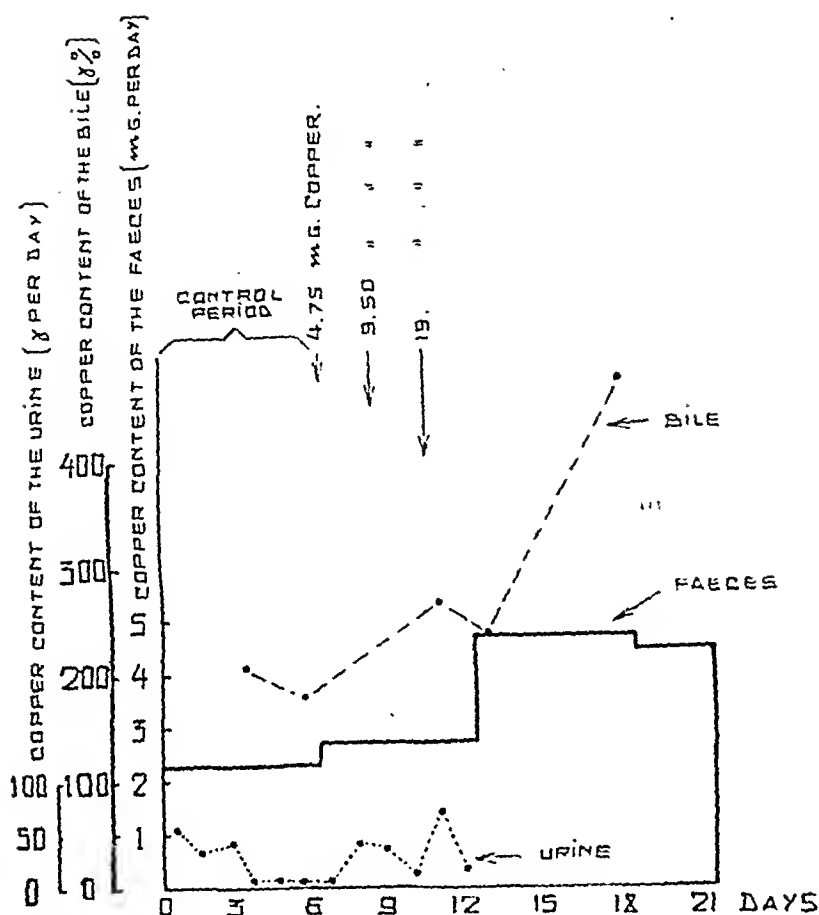


Fig. 7. Excretion of copper in the bile, faeces and urine before and after intravenous administration of copper (ebesal). Test Subject D.

In the bile there was once 205 γ and once 182 γ % found. In the second period, when the copper was injected intravenously, the copper excretion in the faeces only increased a little, in the urine a slight rise was found and in the bile soon after the ebesal injection a noticeable rise in the copper content appeared. This was probably of a temporary nature: at the outset of the third period a level was noted which was only a little above the initial level; a week after the last injection of copper the copper content of the bile appeared to have risen considerably. Only the average copper content of the urine in the third period was determined and it did not appear to have risen compared to the control period. The excre-

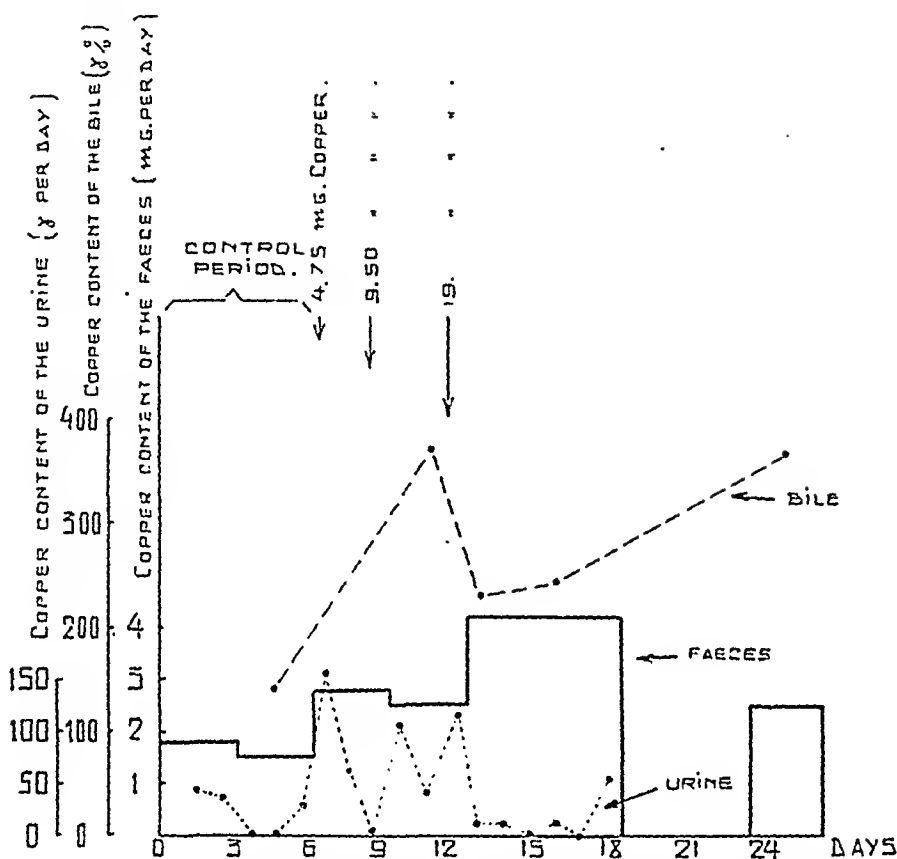


Fig. 8. Excretion of copper in the bile, faeces and urine before and after intravenous administration of copper (ebesal). Test Subject E.

tion of copper with the stools had now indeed risen sharply; in the third period and in the three days following it was about twice as high as in the control period. There was thus a few days after the intravenous administration an excretion of copper via the intestinal tract.

Notes on test subject E (Figure 8).

This test person had particularly regular stools which enabled us with him to take the average of a period of 3 days instead of 6 days for the measuring of the excretion of copper with the faeces. The copper content of the faeces during the control period was low (1.82 and 1.47 mg per day), the test person had a moderate diet.

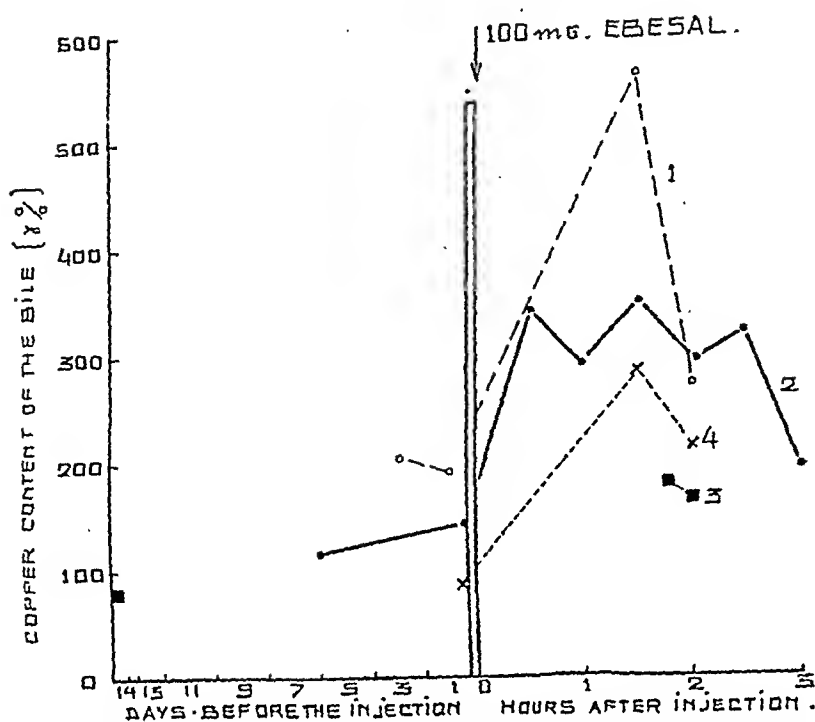


Fig. 9. Copper content of the bile, collected by duodenal drainage, before and after intravenous administration of copper (ebesal).

Here a rise in the copper content of the faeces appeared immediately after the intravenous administration of copper while the excretion of copper with the urine increased noticeably from the 6th to the 12th day; after that the copper excretion with the stools continued to rise, while the copper content of the urine sank below the initial level. From the 24th to the 26th day we investigated the copper excretion with the faeces over again. This had in fact sunk but it was still noticeably higher than the normal level of this test person.

The excretion of copper with the bile was less regular than with the faeces, but showed in any case a noticeably rise after the ebesal injections, this figure does not give the impression that the excretion of copper via the bile runs parallel with that in the stools. This leads one to suppose that the copper which is eliminated from the body with the stools does not come exclusively from the bile but is, at least in part, excreted via the intestinal wall, probably in the colon. As a matter of fact it seems plausible that a more or

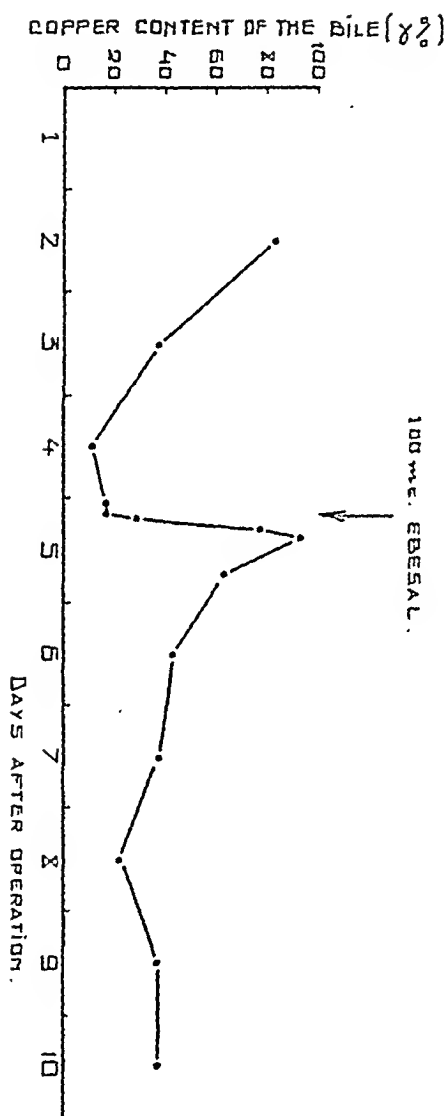


Fig. 10. Copper content of the bile, collected by hepatic drainage, before and after intravenous administration of copper (ebesal).

Notes on test subject B.

Table 5. contains the data on the second experiment person which confirm the results of the first test. Here the copper excretion during the control period was on an average per day 48 γ in the urine and 2.10 mg in the faeces. Of the 114.56 mg of extra copper, which were given in the second period there were excreted in that time 83.07 mg in the faeces and 31.49 mg or 27.5 % were retained. The excretion of copper in the urine did not increase, was actually lower than in the control period.

The excretion of copper with the bile immediately after the administration of copper had ceased, had still scarcely risen but it showed a marked increase later on.

In the third period on an average of 1.72 mg of copper per day more were excreted in the faeces than in the control period. By mistake however just at the beginning of the third period the diet of the test person was increased. Analysis showed that he had received in this way 0.67 mg of copper per day more than in the control period. Even if we assume that all this copper was immediately excreted with the faeces there still remained 1.05 mg of copper per day in the stools which could not have come from the food in this period and which thus probably indicate an excretion of the copper sulphate, absorbed in the second period.

The copper content of the urine also remained low in the third period; nothing can be observed of any excretion by this route of the absorbed copper.

Notes on test subject C.

As may be seen in Table 6 the results of the third test agree very well with those of the two previous ones. With this person in each period we only did a determination of the copper content of the total quantity of urine per period. On an average in the control period 14 γ of copper with the urine and 1.42 mg of copper with the faeces were excreted. This test person had a much stricter diet than A. and B.

In the second period there were here also a total of 114.56 mg of extra copper given. There were 86.62 mg more copper excreted in the faeces than might be expected on the basis of the basal

Summary.

1. A micro method for the determination of copper in blood, bile, faeces and urine is described.

2. If normal persons are given copper *by mouth* for 3 days in the form of 150 mg of copper sulphate per day, only 65 to 75 % of it is recovered in the faeces during the first 6 to 9 days. Probably at least 25 % of it is absorbed into the body from the intestinal tract.

That in any case copper is absorbed through the intestinal wall appears from the fact that a few days after the administration of copper the copper content of the bile rises to more than double the initial level. The normal copper content of the bile (A-bile, drawn with a duodenal tube) amounts to 35 to 205 γ %.

We were not able to demonstrate a rise in the copper excretion with the urine in our test persons. The normal copper content of the urine varies with them from 0 to 12.5 γ %.

Also after the point of time at which it may be assumed that the copper sulphate given has disappeared out of the intestinal tube, the quantity of copper in the faeces remains 1 to 2 mg per day larger than in the control period which preceded the administration of copper. Thus probably the absorbed copper is gradually eliminated from the body via the intestinal tract.

When copper is administered *intravenously* in the form of 100 mg of ebesal (19 mg of copper), the copper content of the blood rises to from 3 to 4 times the initial level. Within 2 to 4 hours however the initial level has been reached again. In that time a temporary rise of the copper content of the bile appears. After a few days the copper content of the faeces rises and probably a rise in the copper content of the bile appears again. The excretion of copper via the bile and the faeces does not appear to run parallel, which makes us suppose that the copper found in the stools at least in part is excreted through the intestinal wall. The excretion of copper with the faeces after three injections of a total of 33.25 mg of copper amounts in the beginning to 2.5 mg per day more than previously. It is thus probable that already within a few weeks by far the greatest part of the copper administered intravenously, has been eliminated from the body.

In the copper content of the urine during the time in which copper injections are given a temporary rise appears.

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Asthenia Crurum Paraesthetica («Irritable legs»).

A New Syndrome Consisting of Weakness, Sensation of Cold and Nocturnal Paresthesia in the Legs, Responding to a Certain Extent to Treatment with Priscol and Doryl. — A Note on Paresthesia in General.

By

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Introduction.

The present communication deals with a disease, or rather a syndrome, which, as far as I can gather, has not been described previously. When the syndrome is complete, it consists of the following symptoms: peculiar and characteristic paresthesia in the lower legs mostly during the night, weakness or clumsiness of the legs while walking, and a sensation of cold in the legs or feet. The paresthesia was called «anxietas tibiæ» in the middle of the previous century but since then seems to have been completely forgotten. Objective signs are lacking. The disease is important from a practical point of view, for it is unpleasant and of long duration, and apparently rather common. It can be treated with success, at least in some cases.

For better understanding of the disease, I shall also give a short description of acroparesthesia and mention a few facts about paresthesia in general.

less large part of the copper in the bile is again absorbed in the small intestine, as is probably the case with the iron from the bile (66).

In Figure 7 and 8 it was seen that the copper content of the bile noticeably increases a few days after intravenous injection of copper.

Moreover we investigated if there were also changes in the excretion of copper in the first hours after an ebesal injection. For this we chose two normal persons (1 and 2) and a patient suffering from rheumatoid arthritis. In the last case we performed the test twice at an interval of two months (3 and 4). As far as possible in these experiments we drew a fresh sample of the bile from the duodenal tube every half hour. The result is to be seen in Figure 9. In each test a noticeable rise in the copper content appeared which reached its maximum within two hours.

Furthermore we examined the bile after an intravenous ebesal injection in a patient on whom a hepaticus drain had been applied after a cholecystectomy on account of cholelithiasis. With this woman also the copper content of the bile rose in the first 24 hours after the injection of copper as may be seen in Figure 10; there the maximum was reached later than with the previous test persons. The noticeable increase of the copper content which we observed in test subjects D and E (Figure 7 and 8) a few days after the intravenous injections, was absent here. Whether this should be attributed to the abnormal condition of the test person which we pointed out on page 184 we cannot say.

We wish here to call attention once more to the great difference existing between the metabolism of copper and iron. After the administration of iron salts by mouth it is well known that the iron content of the serum as a rule rises noticeably (43); an equal dose of copper salt has no influence on the copper content of the blood. After administration of iron either by mouth or intravenously no rise in the iron content of the bile appears and only a slight excretion of iron via the intestinal wall (22, 26, 63); after a dose of copper the copper excretion via the bile and probably also via the intestinal wall rises noticeably.

bled when walking up and down stairs. A fourth often had very painful cramps in one thigh while walking. Symptoms of this nature were lacking in two of the cases. The patients themselves do not pay much attention to the weakness, and it is easily overlooked. Five of the patients complained of *cold feet or legs*, but three lacked this symptom. In one case the lower legs were numb in the morning.

Objective examination has not shown any constant pathologic signs. There is no demonstrable weakness or ataxia in the legs. The reflexes and sensibility are normal. The legs and feet are not cold to touch or discolored. The pulse in the dorsalis pedis artery is good. Oscillometric examination showed normal conditions in one case. The blood pressure was elevated in some cases, but not all. One of the women had varicose veins in one leg. The Wassermann reaction was negative in the five cases where it was studied. The spinal fluid was normal in one case. — Six patients were women and two were men.

Historical Review.

I have not been able to find anything about the syndrome in the literature. The paresthesia, on the other hand, has been briefly mentioned a few times. In Theodor Wittmaack's old monograph of 1861, *«Pathologie und Therapie der Sensibilität-Neurosen»* (1) half a page is devoted to *«anxietas tibiarum»* which is interpreted as *«combined hyperesthesia of the sensible and motor nerves of the legs»*. Wittmaack writes: *«Ein eigenthümliches Gefühl ist die von den älteren Ärzten so genannte Anxietas tibiarum; ein sonderbarer, aber für die Art des Zustandes doch bezeichnender Ausdruck; denn es ist wirklich so, als wäre den zur Zeit damit Behafteten ein Geist der Unruhe und des Bewegungszwanges in die Beine gefahren. Jeden Augenblick bringen sie dieselbe in eine andere Lage . . . In jenem wunderlichen Bilde nervöser Neckereien, welches die Hysterie liefert, findet man häufig auch diesen Zug der unfreiwilligen Unruhe in Beinen und Füßen angebracht. Dieselbe kommt indess auch anderweitig vor, ohne dass man eine bestimmte Ursache dafür aufzufinden vermögte. Ein Freund von mir, kräftiger Mann von vierzig Jahren, wird bisweilen in gelindem Grade davon*

heimgesucht, theils gegen Abend, besonders aber im Bett bis zum Einschlafen. Er muss dann Füße und Unterschenkel jeden Augenblick in eine andere Lage bringen, was er ganz langsam vollzieht, während er in den genannten Theilen eine nicht näher zu beschreibende Empfindung hat, ohne allen Schmerz, ohne Ziehen, am meisten noch einem Gewundenwerden gleichend. Der Zustand hält ungefähr $\frac{1}{4}$ Stunde an.» («A peculiar sensation is the one earlier physicians called *anxietas tibiæ* — a singular but an appropriate name, for it is really as though a restless spirit had flown into the legs of the patients. They change the position of their legs every moment . . . This feature of involuntary unrest in the legs and feet is often seen in the strange conditions brought on by hysteria. But the same unrest is also encountered in other cases, where no definite cause can be found. A friend of mine, a powerful 41-year-old man, suffers mildly from the sensation, occasionally in the evening, but mostly in bed before he goes to sleep. He is forced continually to change the position of his feet and lower legs. He moves them slowly, and in the meantime he has a non-painful sensation in them which he cannot describe exactly . . . The condition persists for about a quarter of an hour.»)

In Bing's «Lehrbuch der Nervenkrankheiten» of 1913 (2), *anxietas tibiæ* is briefly mentioned among the kinds of paraesthesia occurring in neurasthenia. «Als Knochenparästhesie ist der sogenannten, 'Anxietas tibiæ' zu gedenken, eines dumpfen, schwer definierbaren Gefühles in den Unterschenkelknochen, als dessen auch beim Gesunden vorkommende Parallele die bekannte Sensation bezeichnet werden kann, für die der Ausdruck gebräuchlich ist: 'der Schreck ist mir in die Beine gefahren', die aber vom Neurastheniker kontinuierlich empfunden werden kann.» («A form of bone paresthesia which can be mentioned is the so-called *anxietas tibiæ*, a dull feeling, difficult to define, in the shin bones. A corresponding feeling, experienced by healthy persons as well, is the one described as 'my legs became panic-stricken', and which the neurasthenic person may feel continually.»). Bing said that the neurasthenic paresthesiae, like the headaches and sleeplessness, are often exaggerated by the patients. These two quotations are all I can find in the literature about *anxietas tibiæ*. The term is still retained in a few medical dictionaries, but the condition seems to have been entirely forgotten.

I have kept to the old, colorful name »anxietas tibiærum» in the present paper. For the complete syndrome (anxietas tibiærum + weakness and sometimes a sensation of cold in the legs) I should like to suggest the name *asthenia crurum paraesthetica* or »irritable legs». Further experience is needed before it can be decided to what degree the different components of the syndrome may appear independently of one another.

Comparison Between Asthenia Crurum Paraesthetica and Acroparesthesia.

Is there any disease which is characterized by intermittent, mainly nocturnal paresthesia and weakness and clumsiness? Yes, there is at least one, namely acroparesthesia (the syndrome of Nothnagel and Schultze). We shall now compare acroparesthesia with asthenia crurum paraesthetica. First, however, I must give a short description of acroparesthesia, as this common disease is surprisingly little known, and since the word acroparesthesia is occasionally used misleadingly to cover different sorts of paresthesia in the peripheral parts of the body.

Acroparesthesia occurs most often in middle-aged women. The symptoms consist of attacks of numbness, prickling and formication in the fingers or the whole hands, sometimes the whole arms, but seldom in the toes and feet. The numbness which is occasionally attended by pain, develops mainly at night, especially in the early morning. The patients usually rub their hands, wave them about and move their fingers, whereupon the sensation generally disappears in a few minutes. It may be entirely absent during the day, but it is apt to appear on certain movements, e.g., wringing out a cloth, holding a telephone receiver, writing, sewing and, paradoxically, during rest. »I am not able to keep my hands still», said one patient.

My observation has been that the numbness is specially apt to appear when the fingers are holding something firmly (static work¹). When the patient is sewing, for example, it is not infrequently the thumb and forefinger holding the needle which become affected. When the hands and fingers are kept moving (dynamic work¹), they retain their normal sensations. The numbness is always increased by exertion, but it does not

¹ By this expression I refer only to the work of the fingers and hand.

appear until the time of rest after the work or often not until the night. A period of rest nearly always leads to improvement. Thus, roughly speaking, the numbness develops *during* static work and *after* dynamic work.

The fingers may grow white when they become numb, at night as well (Nothnagel's type of acroparesthesia as distinguished from Schultze's which has no visible vasomotor signs), but this happens rarely and, to my mind, the phenomenon should not be confused with blanching of the fingers during the day from cold. In latter case, a combination of two (related ?) syndromes is present — Schultze's acroparesthesia and Raynaud's disease¹.

The fact is often disregarded that *acroparesthesia is often attended by weakness and clumsiness of the hands*, which seem to be independent, in part at least, of the numbness. The patients complain that they drop things they are holding. »I have become lefthanded», said one of my patients. Examination reveals no objective signs apart from reduced dynamometer values. (In Raynaud's disease, the values are normal).

By acroparesthesia I mean *exclusively* the characteristic syndrome just described, *not* the peripheral paresthesia which is experienced in different nervous diseases, e.g. polyneuritis and subacute combined degeneration of the spinal cord.

If we now compare the two syndromes, asthenia crurum parasthetica and acroparesthesia, we find both likenesses and differences. Both diseases are marked by paresthesia occurring mostly at night and alleviated by movement and (though not always?) by a peculiar weakness and clumsiness in the affected members. The course may be long drawn out in both instances. The treatment is partly the same for both, but I shall return to this matter later.

But there are also differences. The acroparesthesia always appears on the periphery. It may, it is true, be situated in the whole forearm or even the whole arm, but in such a case the hand and fingers, too, are always benumbed; the sensation never jumps over the peripheral regions. Anxietas tibiarum is seated in the lower legs, leaving the feet free. Acroparesthesia always comes on late at night, anxietas tibiarum generally in the early night. Another difference lies in the *quality of the sensations*. Acroparesthesia is

¹ I have seen this combination also in a case of pneumatic hammer disease, a fact of theoretical interest.

easy to describe; it is a question of numbness, tingling, a feeling as though ants were crawling on the skin, stiffness; «it feels like when a leg has gone to sleep». The symptoms of *anxietas tibiæ*, on the other hand, appear to be of a more uncommon and peculiar nature, not easy to put in words, obviously because *they cannot be compared with any generally known sensation*. It is something crawling, irritating, unpleasant, deep in the tissues or «inside the bone». Some patients cannot say clearly whether the sensation is painful or not. I can only remember having heard of the same sort of sensation in some cases of posttraumatic pain («troubles nerveux d'ordre réflexe»).

A 53-year-old woman complained that after spraining her wrist she had an irritating, sizzling, creeping, pulsating feeling in her whole arm, «as if the blood seethed and pushed and swept along». It is no real pain but, like *causalgia*, it is alleviated by the tapping on of water. A 37-year-old man reported that, after extraction of a molar tooth in the lower jaw (when the tooth broke and the root was chiselled away several months later), «pain» developed at the angle of the jaw. The «pain» gradually spread to the left side of the head, to the throat, arm and thorax, all on the left side. It was not real pain but an indescribable, unpleasant feeling «inside the bone». It sometimes disappeared. It was worst at night and was aggravated by warmth. It made him nervous. These two cases were reported in a previous paper (3).

The symptoms of these two patients display a striking likeness to *anxietas tibiæ*. To my mind, it is a question of a *special kind of deep paresthesia*, which has hitherto been given little attention.

Despite the existence of certain likenesses, one cannot put *asthenia crurum paraesthetica* and *acroparesthesia* together, in my opinion, for they are *two different, well delimited and characteristic syndromes*.

In this connection, I should like to mention a third syndrome which is also important from a practical point of view but which is little known. It resembles the two other syndromes but cannot be identified with either of them. I refer to the *nocturnal burning pain in the feet* experienced mainly by elderly persons. The feet feel as though they were on fire, especially the soles. The pain comes on, as in the case of *anxietas tibiæ*, a short while after retiral for the night and disappears as the night lengthens. The patients lie and move their feet, hold them outside the bedclothes, or get up and walk, which helps. The feet do not get warm to touch

or red, as in erythromelalgia. In the daytime the feet are generally cold. The arteries of the lower legs may show calcium shadows in roentgenograms, but the pulse in the dorsalis pedis artery is preserved. The syndrome is called «*acromélgie nocturne*» or «*causalgie nocturne spontanée des vieillards*» by Tinel (4), and *pseudo-erythromelalgia* by Craig and Horton (5). There is no generally accepted term.

Therapy.

In five of my cases a rapid and striking improvement was obtained with *Priscol* «Ciba» (benzylimidazoline hydrochloride) in a dosage of one tablet of 0.025 g by mouth three times a day. The nocturnal paresthesia and sensation of cold in the legs decreased considerably. In three cases there was no improvement. In one of them, injections of *acetylcholine* took away the nocturnal crawling sensation for a time, but not the cold and weakness in the legs during the day. Later *Doryl* (carbaminoyl-choline chloride) *per os* 4 tablets a day, greatly relieved all the symptoms in this case.

Most of the patients had consulted several physicians and had been given different medicines, generally narcotics and antineuralgic drugs, to no avail. My series is a small one, but *Priscol* had such a striking effect in some of the cases that I have no doubt that it was the cause of the improvement. Case 2 is particularly convincing. The patient's symptoms had persisted for twenty years and she had consulted several physicians. At first I prescribed fairly powerful evening doses of bromine and phenobarbital, but it did not help. After having taken only *Priscol* for two weeks, however, she came back radiating with happiness and said, «Oh, thank you, doctor, it is the first medicine which has helped me». It cannot have been due to suggestion on my part, for the first medicine I prescribed had no effect, and I did not praise *Priscol* particularly.

As I have shown previously, *acetylcholine* is effective in acroparesthesia, and *Priscol* and *Doryl* also to a certain degree (6, 7, 8). Thus the same drugs seem to be effective both in acroparesthesia and *asthenia crurum paraesthetica*.

Many authors write that *acetylcholine* is so rapidly decomposed that it is useless except when injected in the arteries. This is wrong, for the results are so good in many cases of acroparesthesia, that it must be considered to have an effect, whether or not it can now be explained theoretically.

Description of the Disease (based on 8 cases).

The *paresthesia* is felt in the lower legs (not the feet). It is never experienced superficially in the skin, but deep down in the calf or sometimes the shin. The patient has difficulty in finding the right words to describe it. It is a crawling sensation, irritating and enervating. As a rule it is not a question of real pain. »It is something nervous»; »it makes one nervous». Because of the expression »*anxietas tibiarum*» I have asked the patients whether it is experienced as a kind of anxiety, but they all said no. But all agreed that it was *something very unpleasant*. »It is worse than an ordinary illness», said one woman (case 1) who had nevertheless nearly died both from pulmonary embolism and severe hepatitis. »I hardly dare go to bed», said another woman. The *paresthesia* is mostly felt during the night, generally within an hour after retiral (in one case not until the early morning, however). The sensations disappear or lessen when the legs are moved about, but they soon return. The patients cannot sleep, but are forced to lie and move their legs and continually change their position, to sit on the edge of the bed and kick, or to walk about on the floor. »It is quite impossible to stay in bed.» The *paresthesia* may keep on the whole night, according to the patients at least, but they often disappear in the early morning. They not only prevent the patients from going to sleep, but they can also wake them if they manage to drop off. Two of my patients used to pass the night reading or with needlework. The morbid sensations occur night after night for years, sometimes for decades, and it is no wonder that the patients grow heartily tired of their affliction. During the day, the *paresthesiae* are either entirely absent or are of mild degree, coming on when the legs are kept still, especially in the evenings, e.g. at the theatre or cinema, or if the patients take a nap to try to make up for their lost night sleep. Milder cases also exist where the *paresthesia* is intermittent and of shorter duration (15 minutes to two hours).

The *weakness* is characterized by a heavy feeling in the legs, especially after a long walk; they feel weak and tired and as if they were going to give way. One patient could only walk a short way for this reason. Another said that her legs had given way and caused her to fall hundreds of times. A third said that she sometimes stum-

spinal cord and the numbness developing on pressure on a nerve, for example in the region of distribution of the ulnar nerve if, when the elbow is flexed, the medial epicondyle is rested on a hard surface. The other main type of paresthesia is *discontinuous*, frequently occurring at certain hours or in certain situations, and is often alleviated by rubbing or movement. An example of this type, which we may hypothetically call »angiogenic», is aeroparesthesia. It is to this group that *anxietas tibiarum* belongs.

The paresthesia associated with »*migraine accompagnée*» is intermediate between these two types. It is neurogenic (cerebral) but its cause is a functional, periodic disorder in the brain.

»Angiogenic» paresthesia may also occur in organic nervous diseases. As a matter of fact, it is a fairly frequent accompaniment of these conditions. This is not surprising, in view of the frequency of vasomotor disorders in organic nervous diseases. As examples, I may mention the cold and cyanosis in the involved limbs after cerebral hemorrhage and infantile paralysis. In some forms of organic nervous disease the patient may suffer from both forms of paresthesia. Hitherto, however, I have not seen a case where *anxietas tibiarum* was based on an organic nervous disease.

It is of great practical importance to differentiate between the two types, both from a diagnostic and a therapeutic standpoint. »Angiogenic» paresthesiae are common and usually of no serious import but may, if they are poorly analyzed, lead to a false diagnosis of severe organic nervous disease. Not infrequently they can be successfully treated (acetylcholine, Priscol, novocain blocking, surgical operations on the sympathetic nervous system). The classification is empirical and remains valid even if the hypothesis that the discontinuous paresthesiae are due to a functional vascular disorder proves to be false. The question of the manner of development of the »angiogenic» paresthesiae will not be gone into in the present paper.

Case reports.

Case 1 (private patient). — An unmarried woman, 55 years old, complained that for twenty years she had suffered from unpleasant sensations in her lower legs (not feet) at night. It is an irritating feeling, crawling and annoying, but not a real pain, and nor does it feel like when a leg goes to sleep. It is an extremely vexatious sensation and prevents her from

Pathogenesis.

It is probable that the symptoms of asthenia crurum paraesthetica are produced by a peripheral, functional disorder in circulation. This opinion is supported by the following facts: 1. The symptoms are sometimes favorably influenced by the vasodilative agents Priscol, acetylcholine and Doryl. 2. Five patients out of eight complained of a sensation of cold in their lower legs or feet. 3. In two cases it appears as though the disease developed after or was aggravated by exposure to cold. 4. It resembles acroparesthesia and «acromélangie nocturne», which are considered to be due to vascular disorders. 5. An intelligent woman, who had also Raynauds disease, told me spontaneously that she had the same feeling in her legs, when she recovered from an attack of anxietas tibiæ as in her fingers when «the blood returned» after an attack of blanching.

As regards the weakness in the legs, it is not impossible that it is of the same nature as the weakness in the hands in acroparesthesia (and «troubles nerveux d'ordre réflexe»). It seems to be a particular kind of muscular weakness, of whose nature nothing seems to be known, but whose existence can hardly be denied.

Anxietas tibiæ does not resemble the paresthesia associated with organic diseases but is reminiscent of the paresthesia which occurs in, what may be presumed to be, vasomotor disorders. In order to explain this, I must insert a few lines regarding the two main types of paresthesia.

Two Types of Paresthesia.

A basic rule (which I have never seen mentioned elsewhere) when confronted with a patient with paresthesia is to find out whether it is felt continually or intermittently. «Neurogenic» paresthesia is generally *continual*, examples being the paresthesia in polyneuritis, radiculitis, subacute combined degeneration of the spinal cord and multiple sclerosis. An exception from this rule is the paresthesia which is excited by mechanical forces, such as the Lhermitte paresthesia (a feeling of an electric shock through the trunk and limbs when the patient flexes his head forward) occurring after lesions to the posterior columns of the cervical part of the

sleeping. To alleviate it she has to keep moving her legs. She generally sits on the edge of her bed and kicks, often passing the time with knitting. Or else she paces up and down in the room. The symptoms come on a short while, ten to thirty minutes, after she goes to bed. During the last year they have come on every night, and sometimes persist the whole night, so that she never gets a wink of sleep. Generally they keep up to about five o'clock; occasionally they stop between one and two. Sometimes they wake her. The symptoms have grown worse during the last year and have become particularly severe during the last few months, after hospitalization for severe hepatitis, for which she received injections of insulin, among other treatments. Now they occur almost exclusively at night, but during the first few years they often appeared during the day as well, mostly during the evenings if she sat still, at the theatre for example. Her legs often feel weak and give way under her, and she has fallen down «hundreds» of times during the course of the years. Her legs never feel cold.

She has consulted several physicians. Massage and short-wave therapy were of no help. Fairly large doses of sedatives in the evening only gave a few hours' sleep. She has had high blood pressure for several years but no other disease of interest.

Examination revealed a blood pressure of 215 systolic and 110 diastolic and fairly coarse varicose veins on the left thigh, but nothing else of interest. The feet and the lower legs were not cold to touch or discolored. A powerful pulse was palpated in the dorsalis pedis artery on both sides. The reflexes, sensibility and strength in the legs were normal. The patient looked healthy and appeared sensible and calm on the whole, but she complained bitterly of her disease. She was treated with Priscol, acetylcholine and Gynergen, but without success. Two Dolantin tablets in the evening have a fairly good, though only temporary effect.

Case 2 (Record no. of the out-patient department 1363/43). — An unmarried woman, 67 years of age, formerly a cook, complained of a creeping sensation in her lower legs almost every night for twenty years. It was not a pain, she said, but something «restless», «unpleasant», difficult to describe, situated deep down in the calf, sometimes of one leg and sometimes of the other. The sensation lessened when she kicked with her legs. At the same time (?) she experienced spots of pain in her feet. The «crawling» generally began half an hour after she went to bed and sometimes kept up the whole night. Sometimes it woke her after she had fallen asleep. She usually lay and read or did needlework, or walked about. Occasionally the «crawling» appeared when she sat in the evenings. Her feet always felt cold and she generally had a hot water bottle in her bed. She stumbled easily, especially on staircases. She was also troubled by dizziness, shortness of breath and palpitation of the heart. She had consulted several physicians but had never received any help. A sister of hers suffered from nocturnal burning foot pain. Examination revealed a blood pressure of 180 systolic and 100 diastolic but nothing else of interest.

and consists of an irritating, very unpleasant feeling, difficult to describe. To alleviate the sensation, the patients have to move their legs about again and again. The phenomenon was known in the nineteenth century under the name »anxietas tibiærum», but now seems to have been forgotten.

3. In the daytime the legs feel weak, or tire easily and tend to give way (6 cases out of 8).

4. The feet or the legs often feel cold (5 cases).

5. No objective signs have been demonstrated.

6. The disease can persist for decades.

7. It most closely resembles acroparesthesia (Nothnagel's and Schultze's syndrome), but the two are not identical.

8. It is possible that the condition is due to a functional vascular disorder. In some cases the disease was apparently caused by exposure to cold.

9. In 5 cases out of 8 good results were obtained with benzyimidazoline (Priscol) *per os*.

10. There are two main types of paresthesia, which must be carefully distinguished from one another, the continuous and the discontinuous (»neurogenic» and »angiogenic»). *Anxietas tibiærum* belongs to the latter sort.

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Addition to proof (15. 5. 1944): I have now seen more than 30 cases. Good results were obtained in 7 cases out of 10 with Priscol and in 10 cases out of 14 with Doryl *per os* 4—6 tablets a day.

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(Acting Head: Dr. Bo Ewert, M. D.)

Nitrous Gas Poisoning among Welders using Acetylene Flame.

A study of sixteen cases including four deaths.

By

TORSTEN LINDQVIST, M. D.

(Submitted for publication March 6, 1944).

Introduction.

Acetylene gas is being used in industry on an ever-increasing scale. The metal industry, in particular, is applying it for the purpose of heating metals to high temperatures. This process is necessary in the welding and cutting of metals by means of a gas flame, as well as in the heating of large metal surfaces. Work with welding flames has thus become indispensable at shipbuilding yards and in mechanical workshops.

Poisoning resulting from this type of work has already been described, but considering the widespread application of these processes the number of cases reported is small. Thus Schiötz (1), in 1940, collected 53 cases from the literature, to which he added 3 of his own. Since then, a few more cases have been published (see Lindqvist, 2; Schiötz, 3), bringing the total number of cases mentioned in the literature up to about 75.

As a result of the investigations of recent years the explanation of these cases of poisoning has been largely cleared up, and light has been thrown on the hygienization problems. Experience has shown, however, that many employers have failed to make

themselves acquainted with the results of recent research, and that they are unaware of the causes underlying the accidents that sometimes occur. The patients come to the hospitals for treatment, therefore, without being able to supply any information as to the background of their complaint and the physicians must attempt to diagnose the form of poisoning which may be in question wholly on the basis of the syndrome presented. Unfortunately, the literature contains few references to the syndrome concerned in this species of poisoning. The cases available in which the clinical aspects are treated in any detail are so few that it is difficult to form a satisfactory idea concerning the often very varying symptoms. Using the observations obtained from a series of sixteen patients,¹ and taking into consideration, also, the cases reported in the literature, the present author therefore offers a review of the mode of origin of the complaint under discussion, and a description of the clinical signs and symptoms and the roentgenographic findings. The patho-anatomic aspect also receives attention.

Case Reports.²

Case 1. Out-Patient No. 261/1940. P. O., born 1919. On Feb. 14, 1940, he was engaged in heating rivets; in other words, he was burning out rivets by means of an acetylene welding flame. The work was being done in a confined space in a ship. After working for a short period he developed a headache and a cough and began to feel ill. The next day his cough was worse, and he had a burning sensation behind the sternum and felt faint. As this discomfort was still present on the third day he went to the Sahlgren Hospital on the evening of Feb. 16. His throat was then badly inflamed. A physical examination of the lungs and the heart revealed nothing abnormal. His temperature was normal. The routine examination yielded nothing else of interest.

Owing to my lack of knowledge regarding the syndrome in this form of poisoning, I had no reason to suspect any connection between the patient's illness and his work with acetylene gas, and I therefore interpreted the case as one of benign infection of the respiratory tract. After a couple of days in bed at home he reported that he had completely recovered.

Case 2. Journal No. 1947/1941. H. K., born 1901. On Sept. 30, 1941, he was burning out rivets down in a confined space in a ship. In order to reach the place of work he had to pass through a 7 metre long passage provided with four manholes. No special measures had been taken to ensure

¹ Since this paper was written seven more cases have been encountered.

² Cases 1—10 have already been published in Swedish (2).

ventilation. Another workman who had been engaged on the same job just before him had had to leave the place because he felt ill. When he began to work he noticed a pungent smell, but after that he experienced no discomfort during the hour in which the work was in progress. When he went on deck he felt ill. Some hours later he began to cough and got a headache. In the evening he felt a tingling sensation in the chest and in the night he coughed up a large quantity of thin, pinkish sputum.

On admission to the hospital on the morning of Oct. 1, 1941, his general condition was badly affected. He had a severe cough, and was very short of breath and deeply cyanotic. Temperature, 37.9° C. His throat was red and inflamed. Slight dullness and numerous crepitant râles were to be heard over the base of the left lung. Dry râles were also auscultated all over the pulmonary fields. Physical examination of the heart yielded nothing remarkable. The electrocardiogram was normal. Blood count: Hemoglobin, 114 (by the Autenrieth method); red blood cells, 5.4 million; whites, 9,000. The differential blood count showed a moderate deviation to the left. Sedimentation rate, 7 mm in 1 hour.

Roentgenograms taken immediately after his admission showed, in both lungs, wide-spread, mostly confluent, areas of increased density in the parenchyma; these were situated in all the lobes but were most pronounced in the middle zone. At the apex of the left lung there was an old tuberculosis lesion (fig. 1).

His general condition improved rapidly after cardiac stimulation and the administration of palliatives for the cough. For several days, however, he had severe dyspnea. His temperature, which had been around 38° C on the first day, dropped slowly, and at the end of three days he was afebrile. For a week after the accident he had a persistent headache.

An electrocardiogram taken on Oct. 3 showed normal tracings.

On roentgenograms taken on Oct. 3, only small patches of shadow were visualized, and on Oct. 4 there only remained a pleural mantle and scattered areas of calcification over the apex of the left lung; all signs of the acute condition had disappeared.

On Oct. 10 he was sufficiently recovered to get up, but he was very weak. He was discharged on Oct. 14, and was able to return to work on Oct. 20, three weeks after the accident.

Case 3. Journal No. 1646/1942. S. L., born 1910. A welder. On Aug. 14, 1942, at 7 p.m., he began burning out rivets in the forepeak of a boat. According to subsequent calculations, the volume of the room was 70 cubic metres. There was a manhole in the ceiling which was open the whole time. Compressed air was conveyed to the room at intervals. Other workmen had been burning out rivets in the same room since 4 p.m., but the work had been interrupted for short intervals. After working for a short time he began to suffer from irritation of the throat and nausea, and had to go on deck occasionally to get some fresh air. When on deck he vomited several times. He had not noticed any foreign smell. His cough became gradually worse. When the work was finished, at 12.30 a.m. on

Aug. 15, he felt extremely ill, had a bad cough, and was short of breath, and he could not keep his balance. Owing to the absence of night traffic he was unable to get home at once, and spent the night on a bench in the changing room at the workshop, without being able to sleep and troubled the whole time by his cough and shortness of breath. Next morning he was able to go home on his own, but his wife took him at once to the hospital, to which he was admitted at 9 o'clock on Aug. 15.

On his arrival he was extremely dyspneic and deeply cyanotic, and breathed with a rattling sound. Temperature, 37.8° C. He had a severe headache and his throat was moderately congested. No dullness in the lungs. Crepitant râles were to be heard over the base of both lungs, and at the right base there were also a few friction sounds. Nothing of interest was noted from the other organs at the clinical examination.

An electrocardiogram taken on Aug. 15 showed regular heart rhythm. A—V conduction time, 0.14 sec. QRS complexes and S—T intervals normal. T_{1-3} positive.

On roentgenograms taken immediately after his admission there were visualized cloudy, partly confluent areas of increased density, of a miliary appearance, in both pulmonary fields, but most pronounced on the right side (fig. 2). The lesions were most numerous in the middle zone of the lungs, the apices and bases being of normal appearance. Blood count on Aug. 16: Hemoglobin, 98; red blood cells, 4.9 million; whites, 18,000. The differential blood count showed a moderate deviation to the left. Sedimentation rate on Aug. 17, 28 mm.

The patient's condition gradually deteriorated. On the evening of Aug. 16 his temperature was 39.7° C. The cyanosis and the cough had become accentuated. On Aug. 17 his pulse began to show occasional irregularity.

On an electrocardiogram taken on this date the A—V time was 0.10 sec., the QRS complexes normal, and the S-T intervals somewhat depressed in leads 2 and 3. T_{1-3} positive. On the morning of Aug. 18 he coughed up sputum indicating the presence of edema in the lungs, and this condition grew gradually more acute, despite such measures as venesection, injections of hypertonic glucose solutions and powerful cardiac stimulation. He died at 12.45 p.m. on Aug. 18.

Autopsy (by Dr. C. O. Forsselius): Death stains of normal appearance. Blood blackish-red and greatly coagulated. Heart of normal shape and size. Heart muscle somewhat dry, but its colour was fairly normal.

Lungs distended. The surface of a cut section showed unevenness, with lighter, somewhat elevated patches ranging in size from that of a pea to a hazel-nut, and surrounded by darker, more sunken streaks. On pressure, the entire tissue exuded quantities of frothy fluid. In the larynx and the upper part of the trachea there were no lesions, but in the lower part of the trachea and in the main bronchial branches the mucous membrane was inflamed and displayed petechial hemorrhages. Under the microscope, the entire lung displayed a maximum degree of hyperemia. In the bronchi and the bronchioles there was a purulent process accompanied with epi-



Fig. 1.



Fig. 2.

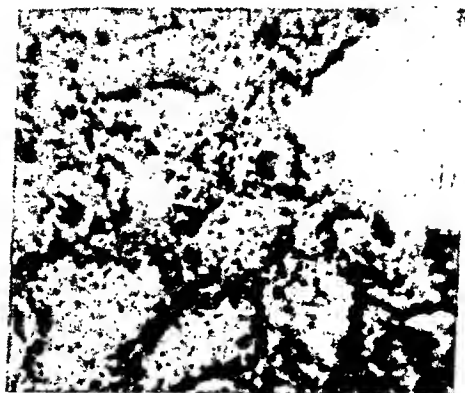


Fig. 3. Two multinuclear cells are visible in middle of the figure.



Fig. 4.

thelial desquamation which had advanced to such a stage that in most places the entire lumen was filled with a mass of cells. A high degree of hemorrhagic edema was present in the parenchyma of the respiratory organs. Over the greater part of the section almost all the alveoli were blocked by this edema, which was combined only to a small extent with epithelium and lymphocytes. The few alveoli that were free were greatly distended, and in some the walls were damaged. In many places there were groups of alveoli in which the edema was accompanied with desquamatory epithelium and a few leukocytes. In these groups, many of the alveoli were completely choked with these cells. The sloughed epithelium was surprisingly well-preserved, and showed no signs of a decreased staining capacity. In many places some epithelial cells took the form of giant cells with 2, 3, 4, or 5 nuclei (fig. 3). Mitotic forms were rare.

The intracranial pressure was much increased. The subarachnoidal fluid was clear. The leptomeninges were hyperemic.

The brain was sent for special examination to Dr. N. Gellerstedt, of the University Pathological Institute, Uppsala, and the following report was received. The white matter of the cerebrum was riddled practically throughout with petechial hemorrhages, the corpus callosum, the white central core of the gyri on the dorsal aspect of the fronto-parietal region, and the middle part of the white matter in the temporal lobes being most affected. The hemorrhages were present all through the capsula interna and down into the peduncles, but they became fewer and smaller through the brain stem. There were no hemorrhages in the cortex, inclusive of the arcuate fibres and the cornu ammonis, or in the greater part of the remainder of the gray matter and the cerebellum, with the exception of a few small patches in the vicinity of the white core of the nucleus dentatus. Histologic examination revealed hemorrhages of various ages, some quite fresh, others showing signs of perivascular, glial proliferation, or "ring" hemorrhages. The process was thus not agonal. In many of the old hemorrhages the central vessel displayed a certain amount of necrosis. The proliferating glia showed signs of fatty infiltration. The endothelium in the capillaries and finer vessels was also noticeably swollen. The ganglion cells in the brain were little changed. Possibly, considering the age of the patient, they contained an undue amount of lipochrome pigment. The walls of the finer vessels were also rich in lipoids.

There were no features of interest in the other organs.

An examination of cadaver parts for medicolegal purposes (by Professor Wolff) yielded no evidence of phosphorus or arsenic in toxic quantities.

Case 4. Journal No. 1654/1942. K. P., born 1895. A rivetter's assistant. He began to work at the same time and in the same room as the preceding patient. He was engaged in rivetting while the others were burning out rivets. From 7 p.m. to 11 p.m. he experienced no discomfort, but towards 11 o'clock he began to feel ill and had to go on deck several times in order to vomit. He had not noticed any pungent smell. When

the job was finished, at 12.30 a.m., he felt too ill to go on working. He rested for a couple of hours and then went back to work in the open air until 6 a.m. Soon after this he began to get a cough and felt very faint. On the following days he felt weak, coughed a lot, and had a bad headache. These symptoms were sufficiently severe to cause him to stay in bed part of the time. On Aug. 17 he had a morning temperature of 38.4°C , and he was sent to the hospital by his employers. He was then in an exhausted condition, became noticeably breathless on the least exertion, and was blue about the lips. He had a troublesome cough but no sputum. His throat was not inflamed. At the physical examination of the lungs there were numerous dry râles basally on the right side, but no other signs of abnormality. No pathologic signs from the other organs.

Blood count: Hemoglobin, 89; red blood cells, 4.5 million; whites, 10,000, with a slight deviation to the left. Sedimentation rate on Aug. 18, 12 mm.

On the roentgenograms taken immediately after his admission there was scattered dark mottling of irregular outline over the greater part of both pulmonary fields, but concentrated chiefly in the middle zones (fig. 4).

The QRS complexes showed signs of notching, on an electrocardiogram taken on Aug. 18, but there was nothing definitely abnormal about the tracings.

During the first week he was subfebrile, and after that afebrile. His cough soon disappeared but for a long time he had little strength. It was not until Sept. 8 that he was able to get up.

The lesions visualized on the roentgen pictures had already noticeably receded by Aug. 18 (fig. 5). By Aug. 24 there were no further signs of changes in the parenchyma, but the left hilus was seen to be still enlarged. This abnormality had also disappeared on the roentgenogram of Sept. 3.

The sedimentation rate had risen to 41 mm on Aug. 24, but by Sept. 8 it had fallen to 7 mm.

He was discharged on Sept. 10 and resumed his work on Sept. 21. At a follow-up examination on Nov. 21, 1942 he reported complete recovery. The electrocardiographic tracings were still the same as they were on Aug. 18.

Case 5. Out-Patient No. 658/1942. O.P., born 1897. An iron — plate worker. He had often suffered from the same symptoms, although in a milder form, after working with acetylene gas, as those he had now experienced. The last time had been in February 1942 when he and several of his workfellows had had to stay at home for a few days.

On Aug. 14, 1942 he began burning out rivets at 4 p.m. in the same room as that in which the two preceding patients later worked. At first he noticed a musty smell in the room, but during the course of the work he smelt nothing pungent about the air. He felt no discomfort until 10 p.m., when he began to get a headache and a sensation of heaviness in the chest.

When he went on deck he vomited and began to cough. Despite the cough, he went on working until 1 a.m. on Aug. 15. The next two days he stayed away from work because he felt weak and ill, and had a cough. On Aug. 17 he reported for work, but was sent to the hospital for an overhaul because he did not feel well.

His general condition was not particularly affected. No dyspnea or cyanosis. His throat was not inflamed. At the physical examination of the lungs a few soft râles were to be heard at the bases. There were no other findings of interest from the clinical examination. His temperature was normal. Sedimentation rate, 15 mm.

On roentgen films taken on Aug. 17, strands of increased density and a few patches of infiltration with fairly indistinct outlines were to be seen in both lungs. A pleural mantle was visualized at the apices and streaky infiltrations on the right side.

He was kept in bed at home and examined at short intervals. The cough persisted for a week, and the headache, which he had for a whole month after the mishap, gradually diminished in intensity.

On a control roentgenogram taken on Aug. 19 the lesions in both pulmonary fields had begun to clear up (with the exception of those at the right apex, which were interpreted as being of earlier origin). The same picture was seen on Aug. 21 and Aug. 24, and not until Aug. 29, two weeks after the accident, were the films practically free from the miliary infiltrations. The sedimentation rate had by that time dropped to 5 mm.

He had been afebrile during the entire period. It was not till Sept. 28 that he could resume his work.

Case 6. Out-Patient No. 659/1942. E.B., born 1918. A rivetter's assistant. In company with the preceding patient he had begun to burn out rivets on Aug. 14, at 4 p.m. He had often been sent on deck, however, while the work was in progress. He began to feel ill around 8 p.m. About one hour later he began to suffer from a cough, shortness of breath, and a headache, and had to go on deck time after time to be sick. However, he kept on working till 12.30 a.m. on Aug. 15. On the way home his cough was bad and he coughed up a small amount of blood. He stayed at home and rested on Aug. 15 and 16, during which time he suffered from the cough, shortness of breath, and a headache. On Aug. 17 he reported for work, but was sent to the hospital for an examination. He appeared to be weak and exhausted, and had a moderately severe cough. His throat was violently inflamed. A few soft râles were to be heard at the base of both lungs. No other clinical findings of interest. Sedimentation rate, 3 mm. No abnormal features were noted on the roentgen films.

He was recommended to rest quietly at home. At an examination on Aug. 20 he was still very weak and suffered from a headache. His cough had not entirely disappeared. After that date he made a rapid recovery and could resume his work on Aug. 25.

Case 7. Out-Patient No. 657/1942. H. P., born 1915. A rivet heater. In company with patients 3 and 4 he began to work in the same room on

Aug. 14 at 7 p.m. After about an hour's work he felt constriction in the chest and a headache, and had to go on deck to get some fresh air. He soon began to cough. When the job in the forepeak was completed, at 1 a.m., he did other work on deck until 6.30 a.m. He then went home and stayed there for two days because he felt weak and had a cough. On Aug. 17 he was ordered to report to the hospital for examination.

He appeared to be weak, was a bad colour, and had a moderately severe, rapid tremor which had developed since the accident. His throat was mildly red. There were soft râles at the base of both lungs. The usual clinical and neurologic examinations revealed nothing remarkable. Sedimentation rate, 4 mm. Roentgenograms of the lungs were normal.

His cough disappeared within a couple of days, but he was slow in regaining his strength. He returned to work on Sept. 3. There was then no manifest tremor.

Case 8. Journal No. 2169/1940. G.A., born 1896. A filer. On Nov. 29, 1940 he was engaged together with two other men in loosening the tiller from the rudder-stock on a warship docked for repairs. They were heating the tiller to make it expand so that it could be more easily removed. The work was being done in a space having a volume of about 150 cubic metres. It was connected by a hatch, 1 metre square, with an upper room with open windows. In addition to this there was an air-pipe with compressed air running to the place of work down a stairway from the deck, two floors up.

The tiller was painted, and when they began to heat it by means of two large flames a thick smoke was produced. This poured up through the hatch into the upper room in which the patient was working. He carried on for half an hour in this smoke, wearing a gas-mask. The heating process was then discontinued and he worked in the lower room without a mask. A few hours later the heating was started again and the same smoke rolled up. Once again the patient worked in the upper room wearing a gas-mask. Half an hour later the process was broken off and he went back to the lower room, wearing no mask. The heating and the work following it was repeated a third time, but now, after five hours, he began to suffer from a bad cough, nausea, and breathing difficulties. The cough had already made its appearance after about an hour's work.

The symptoms persisted after he went home, and during the night he could not sleep on account of shortness of breath and the cough.

He arrived at the hospital on the following morning, Nov. 30, in a badly affected condition and with dyspnea even when at rest. His face was deeply cyanotic, and he had bad coughing attacks but no sputum. His throat was noticeably inflamed. Numerous light râles were to be heard all over both lungs. The clinical examination brought out nothing else of interest. He had no fever on his admission but during the next few days his temperature rose to 38° C.

Blood count: Hemoglobin, 108; red blood cells, 5.3 million; whites, 11,000. The differential blood count showed a moderate deviation to the left. Sedimentation rate, 4 mm.



Fig. 5.



Fig. 6.



Fig. 7.

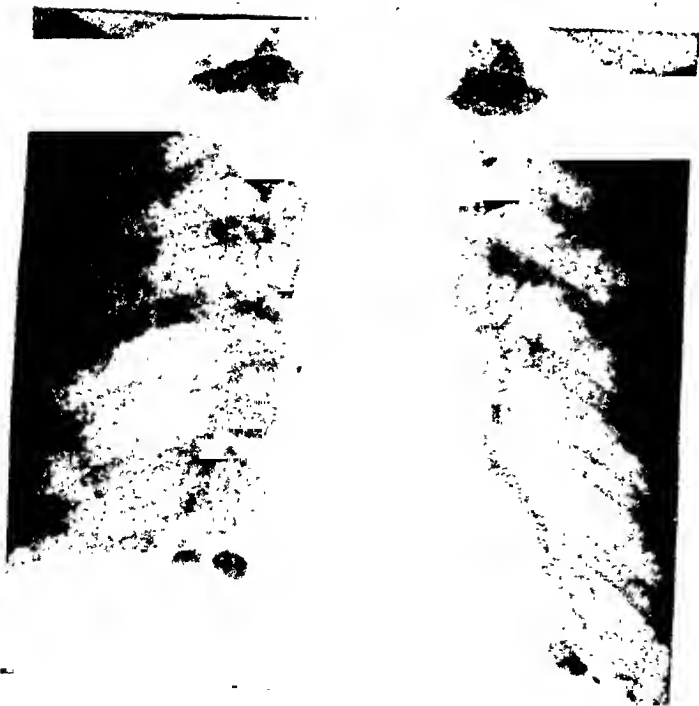


Fig. 8.

On roentgenograms of the lungs taken on Dec. 3 there were military and streaky infiltrations, in places confluent, in both pulmonary fields except for the apices (fig. 6). On Dec. 5, only two days later, these lesions had receded noticeably, leaving only military shadows (fig. 7).

His temperature fell slowly until by Dec. 9 he had no fever, and his general condition had improved. He then became worse again, his temperature gradually became elevated, the cough, shortness of breath, and cyanosis increased, and on Dec. 14 and 15 his condition was as affected as it had been on his admission. At the base of the right lung dullness and weakened respiratory sounds were heard, and basally in both lungs there were soft râles. Roentgen examination on Dec. 18 revealed that the infiltrations had increased and that the right sinus was filled (fig. 8). The sedimentation rate, which had previously been low, rose to 15 mm on Dec. 18, and to 24 mm on Dec. 23. He picked up again, however, but he was not without symptoms of fever until Dec. 28. He got up on Jan. 3, 1941. He was then still suffering badly from breathlessness. A few lesions were still to be seen on the films of the lungs at the beginning of January, but they had disappeared by Jan. 15, when he was discharged.

An electrocardiogram taken on Jan. 13 indicated left ventricular preponderance but no other signs of abnormality.

He returned to work on Mar. 1, and has since then been able to carry on, but he easily becomes breathless. Before his mishap he never had breathing difficulties.

Case 9. Out-Patient No. 1417/1940. E. P., born 1905. A filer. He was a member of the same gang, and worked the same hours, as the preceding patient, but he was in the lower room the whole time, manipulating one of the flames. During the actual heating process he wore a gas-mask, but he noticed a pungent smell and thinks that gas must have penetrated the mask. In the intervals between the heatings he wore no mask. After a couple of hours' work he got a bad cough. On the evening of the same day the cough got worse, and he felt a prickling sensation behind the sternum, and became very breathless. On account of this discomfort he stayed at home during the next few days. He thinks he had a temperature.

On Dec. 3 he went to the medical Out-Patient Dept. and was then found to be afebrile. His throat was bright red. Scattered dry râles were heard in the lungs. Sedimentation rate, 30 mm. Nothing else of note was observed.

At the roentgen examination on Dec. 3 reticular mottling was seen in both pulmonary fields. Another examination on Dec. 5 yielded completely normal films.

He was treated at home and kept in bed at first. The cough and breathing difficulties gradually subsided. By Dec. 11 the sedimentation rate had dropped to 8 mm. He resumed his work on Dec. 19.

Case 10. Out-Patient No. 327/1940. B. S., born 1898. A mechanic. He was working together with the two preceding patients and under exactly the same conditions as case 9. During most of the time the heating was

in progress he wore a gas-mask, but for a short time he worked without it. He then got an irritating cough. During the next few days he had a troublesome cough and slight difficulty in breathing. He went on working, however, despite a feeling of weakness. As the breathing difficulties persisted he came to the Out-Patient Service on Dec. 5.

With the exception of slight cyanosis nothing abnormal was observed at the routine clinical examination. Roentgenograms of the lungs were normal.

The symptoms subsided rapidly under the influence of rest, and he returned to work on Dec. 10.

Case 11. Journal No. 158/1943. S. A., born 1919. A plater. On Jan. 20, 1943 he was engaged in burning out rivets in a small tank having a total volume of about 30 cubic metres but divided into compartments by low partitions. The flame he was using was small, and the work was being done in short shifts. In the afternoon he began to cough and to have difficulty in breathing, but after he stopped work at 4 p.m. he had no further trouble. He went back to the same work at 7 a.m. the next day. After the flame had been burning continuously for half an hour he got such a bad cough that he had to stop work and go on deck. He was sent at once to the hospital, to which he was admitted at 8.45 a.m.

He was then deeply cyanotic, breathed heavily, and had an irritating cough. His throat was not inflamed. No signs of abnormality were noted either from the lungs or from other organs at the physical examination.

The lungs were roentgenographed immediately on his arrival and were found to be normal. Four further roentgen examinations carried out during the next twenty-four hours gave the same result.

He was put to bed and given an alleviating medicine for the cough. After about an hour the cough subsided and he had no further discomfort. He was able to leave the hospital the day after being admitted, and on Jan. 28 he returned to work.

The blood picture had showed no disturbances, and the electrocardiogram was normal.

The following two cases were placed at my disposal through the courtesy of Dr. Claes Grill, head physician at the Borås Central Hospital.

Case 12. E. A., born 1899. A plater. On Jan. 20, 1943 he was working inside a metal cylinder 1.5 metres in diameter and 4.4 metres long. In addition to a manhole of 300 × 400 mm there was one hole with a diameter of 75 mm, two of 65 mm, one of 33 mm, and one of 15 mm. With the manhole shutter closed, its edges were being heated by means of a large acetylene flame. After ten minutes' work the patient felt ill; the hole was therefore opened and he came out into the fresh air. A compressed air tube was then drawn into the cylinder through one of the other holes and the work was continued with the manhole shutter closed for a further 5 to 10 minutes. He felt ill and breathless after this period also. He did

other work for one more hour and then bicycled home and back again in heavy, slushy snow. On his return, he seemed breathless and a little later he complained of a cough and a headache. He went on working, finishing about five hours after the completion of the job in the cylinder, and then went home. On his arrival he felt a constriction in his chest, and pain when breathing, and was therefore taken at once to the Borås Hospital.

On admission his general condition was little affected; he was slightly breathless but not cyanotic. His throat was pale. Tachycardia was present, 130 beats per minute, but there were no other signs of abnormality from the heart. In the night, about 12 hours after being exposed to the welding flames, he became worse and coughed up bright red, frothy sputum. He improved after oxygen therapy. At noon the following day he was worse again, with severe dyspnea, but he rallied after venesection and administration of oxygen. He deteriorated as soon as an attempt was made to discontinue the oxygen treatment. At midnight he suddenly became worse and died during a severe attack of laboured breathing, 36 hours after exposure to the welding flames.

On his admission to the hospital his temperature was 39.1° C, but the following day he was slightly subfebrile. Blood count: Hemoglobin, 109; red blood cells, 5.46 million; whites, 15,700, with a marked deviation to the left. An electrocardiogram taken on his arrival was normal. Sedimentation rate, 2 mm.

At *autopsy* the lungs were found to be emphysematous without macroscopic signs of pneumonie foci. They contained a large amount of frothy fluid. The gross appearance gave no indication of other abnormalities.

Histologic examination (by Prof. O. Reuterwall, Stockholm) yielded the following information. Advanced edema was present in the parenchyma of the lungs. The alveolar septa were swollen and the capillaries distended with blood, and in places leukocytic infiltration was to be seen. In some of the lumina of the alveoli there were numbers of polymorphonuclear leukocytes, and in some, red blood corpuscles and fibrinous effusion. A number of multinuclear epithelial cells of the same type as those seen in case 3 were also present. — In the bronchial lumina there was abundant mucus mingled with desquamatory epithelium and polymorphonuclear leukocytes. The epithelium in the mucous membrane of the trachea was normal. Edema and a moderate degree of round cell infiltration was present under the epithelium. — Apart from the fact that the blood vessels were overfull there was nothing remarkable about the heart, liver, or kidneys.

The brain was examined by Dr. N. Gellerstedt, from Uppsala. Nothing definitely pathologic could be demonstrated either grossly or under the microscope.

Case 13. O. P., born 1912. A mechanic. He was working together with the preceding patient on Jan. 20, 1943, and spent the same length of time in the cylinder. He felt ill and breathless but these symptoms soon passed over. He also had slight irritation of the throat, which persisted.

He worked as usual for the rest of the day. In the evening the cough got worse and he had pains behind the sternum. The following night he was unable to sleep on account of the cough and laboured respiration. When he arrived at the Borås Hospital the next day at 10 a. m. his general condition was much affected, he had severe dyspnea and was deeply cyanotic. He complained of pains over the cardiac region and had an acute, irritative cough. His throat was not irritated. Numbers of light râles were to be heard over the lungs. Nothing unusual from the heart. In the afternoon his breathing became more laboured but he responded favourably to cardiac stimulants and oxygen. The whole of the following day he was poorly. After a bloodletting he improved noticeably. During the next few days he made a rapid recovery and was discharged on Feb. 1. Because of persistent weakness, however, he was unable to resume his work until Feb. 22.

During the first days at the hospital he was subfebrile. Highest temperature, 38.7° C. Blood count on admission: Hemoglobin, 100; red blood cells, 4.58 million; whites, 8,100.

Electrocardiograms taken on Jan. 21 and 23 showed normal mechanism.

Roentgenograms of the lungs taken on Jan. 24 were normal. Sedimentation rate, 10 mm on Jan. 22, 21 mm on Jan. 30, 11 mm on Feb. 6.

The following case included through the courtesy of Prof. Nanna Svartz, of Karolinska Sjukhuset, Stockholm.

Case 14. S. A., born 1910. A locksmith. In 1932—1933 he had been treated for pulmonary tuberculosis, during which time a thoracoplasty had been done on the left side. He had since then appeared to be perfectly well. On Mar. 2, 1942, at 5.30 p.m., he began a training course in gas-welding at a welding school in Stockholm. The work was being done in a well-ventilated room about 770 cubic metres in volume. It lasted till 9.30 p.m. and during that time he experienced no discomfort. On arriving home on the evening of the same day he complained of nausea and a headache. During the night he vomited repeatedly. The following morning he felt extremely exhausted, breathed heavily and wheezily, and was deeply cyanotic.

On admission to Karolinska Sjukhuset on the morning of Mar. 3 he was almost unconscious, and extremely cyanotic and dyspneic. Moist râles in great quantities were to be heard over both lungs. A high degree of tachycardia was present. The râles prevented anything further from being obtained from the heart, and because of his generally poor condition a more thorough examination could not be made. After administration of oxygen and stimulation of the heart he showed some improvement, but around 4 p.m. the pulmonary edema became worse. He rallied slightly after venesection, but at 5 p.m. attacks of general cramp lasting several minutes set in, and he finally ceased to breathe, a large quantity of frothy, bloody sputum gushing out of the mouth.

The autopsy was carried out by Prof. W. Bosaeus, and yielded the following information. The right pleural cavity contained 175 cm³ of clear,

dark-red fluid. The left lung was adherent to the chest-wall. The right lung was heavier than normal, and was edematous, especially towards the posterior aspect. At the apex there was an old tuberculosis lesion, showing scars and a pea-sized, cementified core. The left lung was also edematous, and contained scars and numbers of small, cementified foci as a result of an old tuberculosis. Under the microscope the lung was seen to be extremely hyperemic, and the alveoli were edematous and filled with a serous fluid which in places contained a few red blood cells. The alveolar epithelium showed a certain amount of desquamation, and contained a few multinuclear cells. The bronchi were full of a secretion rich in sloughed epithelial cells which incorporated leukocytes and a few isolated red blood cells. Most of the epithelium in the bronchial mucous membrane had sloughed. A certain amount of round cell infiltration was present in the tunica propria. The epithelium in the tracheal and laryngeal mucous membranes had dropped off, and the tunica propria in these organs displayed excessive hyperemia, some edema, and a fair amount of round cell infiltration. — The heart was of normal size. Under the endocardium in the left ventricle there were observed a few hemorrhages the size of a pin-head, some of which were confluent. No other gross or microscopic changes in the heart. — The pial vessels contained much blood. The white matter in the cerebrum was noticeably blood-flecked. As regards the microscopic appearance also, the blood vessels in the pia and the arachnoid, as well as in the brain substance, were overfull of blood. In these parts also, small isolated hemorrhages were to be seen, and here and there a fair degree of edema. — In the stomach, especially inferiorly, there was copious petechial hemorrhage, but the mucous membrane in the other parts of the alimentary canal showed no definite changes. — Grossly, the liver appeared to be normal, but microscopically a slight increase in fatty infiltration was observed in the liver cells. — The kidneys seemed normal to the naked eye, but the histologic examination proved that the malpighian bodies had been converted to a large extent into hyaline balls. — No abnormal features in the other organs.

Examination by a public analyst revealed no signs of ethyl alcohol, methyl alcohol, metals, or phosphoretted hydrogen.

The following cases were supplied by Prof. Malte Ljungdahl, of the Malmö General Hospital.

Case 15. K. L., born 1913. A welder. On Mar. 3, 1943 he had been working inside a cement-coated fresh-water tank having an approximate volume of 30 cubic metres. The only ventilation provided was a 30 × 50 cm manhole. The wall-plates were being heated with an acetylene flame in order that the surface irregularities could be evened out with a sledge. The burner was alight only for a few minutes at a time. The work was begun at 8.30 a.m. After a very short time he felt ill and had to go out into the fresh air, but he went back to his work at once. After a while he began getting attacks of coughing and breathlessness, and he was therefore trans-

ferred after a couple of hours to a larger tank with a volume of 100 cubic metres, where he worked till 4 p.m. without further discomfort. Shortly after this he felt ill, and in the evening he complained of a cough and pains in the chest. In the night his breathing was laboured and he coughed up blood-streaked sputum.

The next day at 10 a.m., when he arrived at the Malmö General Hospital, his general condition was badly affected, his face was cyanotic and his breathing rapid (70 per minute). He groaned at every breath. The mucous membrane in the throat was red and cyanotic. Numbers of loud, loose or hard, bubbling and crepitant râles were heard all over the lungs, but especially at the bases and anteriorly on the left side. The heart could not be auscultated because of the sounds from the lungs.

Electrocardiographic examination: 135 beats per minute; A-V conduction time, 0.14 sec.; QRS complex, 0.08 sec.; S-T interval normal. T_{1-3} positive. Thus, a normal mechanism.

Blood count: Hemoglobin, 114; red blood cells, 5.75 million; whites, 19,300, and a moderate deviation to the left.

Temperature on admission, 38.7° C.

He reacted favourably to venesection but the dyspnea and cyanosis soon became worse again and he coughed up quantities of bright red, frothy phlegm. A second attempt at venesection was unsuccessful since the blood displayed a greatly increased tendency to coagulate. He died at 12.45 a.m. on Mar. 5.

Autopsy (by Prof. A. Lindau): The mucous membrane in the trachea was moderately inflamed. Petechial hemorrhages in large quantities were present in the posterior parts of the lungs. Posteriorly, the lungs were dark red and devoid of air, while on the anterior aspect they were lighter and displayed frothy edema. In section, maximal degree of edema was to be seen. Microscopically, the pulmonary alveoli were filled with an acute edema. Between the edematous areas there were sections of air-containing parenchyma. Here and there the alveolar walls showed leukocytic infiltration; this was spreading sparsely into the alveoli, in which beginning precipitation of fibrin was also observed. Sloughed epithelial cells, some of them multinuclear, were also present in the alveoli. No morphologic changes were apparent in the vessels or the bronchial tubes. — The heart was somewhat broadened. Subendocardial, punctate hemorrhages were noted in the left ventricle. — The brain was extremely hyperemic but there were no gross signs of hemorrhage. Microscopic examination of the brain was not undertaken. No abnormal features apparent in the other organs.

Case 16. K. N., born 1920. A hodman. On Mar. 3, 1943 he was acting as an assistant to the preceding patient, and under the same working conditions. He also felt ill after a short time in the tank and had to go out into the air. At about the same time as the other patient he also began to cough and have breathing difficulties. As soon as he stopped work in the confined space, at 11.30 a.m., however, the discomfort subsided and he

did heavy work until 4 p.m. Later in the day he began to suffer from shortness of breath and pains in the chest and abdomen which were so severe that he could hardly sleep that night. Next morning he vomited and felt too ill to get up. He coughed up blood-streaked sputum and had a troublesome headache.

When he was admitted to the Malmö General Hospital at 2 p.m. on Mar. 4 his condition was not much affected. His face was slightly cyanotic, however, and he became short of breath on the slightest exertion. His throat was moderately red. A great many fine and fairly coarse râles, of both the moist and the consonating variety, were heard over the anterior surface of the lungs. Posteriorly, the râles were scarce. Nothing else of interest was found at the routine examination.

Blood count: Hemoglobin, 99; red blood cells, 4.97 million; whites, 10,000, and a slight deviation to the left. No carbon dioxide could be demonstrated in the blood. Sedimentation rate on Mar. 4, 6 mm.

His symptoms soon subsided. On the first days after his admission he was slightly subfebrile, and after that afebrile. He left the hospital on Mar. 11, and returned to work on Mar. 20.

Roentgenograms of the lungs taken on Mar. 9 were normal.

Discussion.

1. *The cause of the poisoning.* As this problem has been discussed in detail by Schiötz (1, 3), I shall only treat here certain aspects bearing directly on the cases reported in the present paper.

Through the investigations of a number of authors, the most thorough of which are those of Rimarski and Konschak (4), it has been proved that when an acetylene flame is burning in a confined space, nitrous fumes are formed in sufficient quantities to be dangerous. The conditions under which the patients in the present series were working when they became affected were also such as to give every justification for assuming that in most instances nitrous gases were present in large quantities. According to Rimarski and Konschak, a concentration of nitrous fumes capable of causing death can be produced in a space having a volume of 20.7 cubic metres, with a large flame burning for 15 minutes. In cases 12 and 13, the patients were working inside a cylinder with a volume of only 10 cubic metres. In some of the other cases the volume of the room was about 30 cubic metres. That nitrous gas poisoning could occur in these cases is obvious. In another experiment, Rimarski and Konschak demonstrated that a toxic concentration of nitrous fumes can also be produced in a space having

a volume of 75 cubic metres even when a ventilator is in use, if an acetylene flame is kept burning for 20 to 30 minutes. It is not to be wondered at, therefore, that symptoms developed in the patients in my series (nos. 3—7) who were working for hours in a space 70 cubic metres in volume and using an acetylene flame during the greater part of the time.

It is evident, therefore, that at least in the majority of my cases nitrous gases could have been the cause of the symptoms. It remains to be discussed, however, whether other substances might have been contributory genetic factors.

As purified acetylene in cylinders was used in every instance, poisoning with AsH_3 or PH_3 , which substances have been thought by earlier investigators to be the cause of this type of mishap, can not have been in question in the present cases. (Cf. Schiötlz, 1, 3). Nor it is likely that carbon monoxide was a contributory factor, since Rimarski and Kenschak (4) have demonstrated that CO can not be evolved in dangerous concentrations under the conditions prevailing in my series. Earlier authors have come to a different conclusion, however (e.g. Macnicke, 5; Mawick, 6, 7, 8), and the question of CO as a possible cause of the poisoning will therefore be discussed in more detail in connection with the clinical and patho-anatomic findings. In most of the cases the welding flame was being used to heat surfaces of pure iron or a cement-coated surface, and thus fumes arising from the piece of work under treatment could not be said to be responsible for the symptoms. Cases 8 to 10 constitute exceptions in this respect, however, and in view of the other circumstances in connection with these cases poisonous substances other than nitrous gases might have been present.

Rimarski and Kenschak (4) state that the use of an acetylene flame involves no great danger in rooms of more than 100 cubic metres in volume. The three last-mentioned patients had been working in a space of 150 cubic metres, and furthermore, while the burner was alight, the man most affected had been the whole time in a well-ventilated room situated immediately above. Besides this, they had all worn gas-masks while the work was in progress. They stated that when the painted surface became hot from the flame a thick smoke with a pungent odour was produced. There was reason to believe, therefore, that some gas with toxic properties might have been evolved from the paint. Because of this pre-

and consists of an irritating, very unpleasant feeling, difficult to describe. To alleviate the sensation, the patients have to move their legs about again and again. The phenomenon was known in the nineteenth century under the name »anxietas tibiaram», but now seems to have been forgotten.

3. In the daytime the legs feel weak, or tire easily and tend to give way (6 cases out of 8).

4. The feet or the legs often feel cold (5 cases).

5. No objective signs have been demonstrated.

6. The disease can persist for decades.

7. It most closely resembles acroparesthesia (Nothnagel's and Schultze's syndrome), but the two are not identical.

8. It is possible that the condition is due to a functional vascular disorder. In some cases the disease was apparently caused by exposure to cold.

9. In 5 cases out of 8 good results were obtained with benzylimidazoline (Priscol) *per os*.

10. There are two main types of paresthesia, which must be carefully distinguished from one another, the continuous and the discontinuous («neurogenic» and «angiogenic»). *Anxietas tibiaram* belongs to the latter sort.

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Addition to proof (15. 5. 1944): I have now seen more than 30 cases. Good results were obtained in 7 cases out of 10 with Priscol and in 10 cases out of 14 with Doryl *per os* 4—6 tablets a day.

sumption, the paint on the surface of the metal was subjected to careful analysis. The analysis was carried out by S. Toresson, an analyst at the laboratory attached to the Götaverken Shipbuilding Yards, and he found that the coating of colouring matter contained heavy spar, zinc oxide, zinc sulphide, iron and aluminium oxides, and an organic substance (dried oil or lake). There were only traces of calcium, lead, chlorine, and arsenic, and no phosphorus at all could be detected. A further examination by Prof. G. Ljunggren of the Defence Department's chemical section revealed that on dry distillation of the paint acrolein was formed in large quantities. In addition, there was produced a thick smoke with an irritant action and containing zinc oxide and other substances.

Acrolein, C_2H_3COH , is evolved from glycerine during the process of heating, and it may have been formed, at the time of the mishap, from glycerine in the paint. Even in very low concentrations it has a highly irritant action on the conjunctivae and the upper respiratory tract, and in larger amounts it may also cause pneumonia. During the previous World War it was used in poison gas attacks. Cases of supposed acrolein poisoning following acetylene welding have been described by Koelsch (9).

Thus, as acrolein was produced in large quantities while these three patients were at work, and since the syndrome bore a resemblance to that occurring in acrolein poisoning, it is not beyond reason that this gas may have been partly responsible for the symptoms. It should be noted, however, that the patients had neither a discharge of tears nor nasal catarrh, but only a cough, and a certain hesitation is felt, therefore, in assuming that the genesis in these cases could have differed from that of the others.

While it is thus evident that the patients referred to in the case reports had been subjected to the influence of nitrous fumes, yet before the etiologic factor can be definitely established it is necessary that the clinical symptoms and signs, and the patho-anatomic appearances, should coincide with the findings already made in proved cases of nitrous gas poisoning.

2. *The clinical syndrome.* The first symptoms generally appear even while the work is in progress. They consist as a rule of a cough and nausea. The cough is not necessarily one of the initial symptoms, however (see cases 2, 4, & 12), and in some instances it can be insignificant. The nausea, which is often accompanied by

vomiting, is sometimes the dominating feature, but it may also be absent (cases 7—11). In some of the patients a headache developed at an early stage (cases 1, 5 & 7). As regards case 14, the patient reported that no symptoms at all had arisen during the course of the work, but his statements are somewhat vague.

If a man experiencing these symptoms stops work at once and is given suitable treatment, no further discomfort need arise. An example of this is provided by case 11, in which, despite the violent initial symptoms, there was no further development of the illness.

In the majority of the cases, the first symptoms either subsided or totally disappeared as soon as the men were removed from the influence of the dangerous fumes. After an interval which varied in the individual cases symptoms reappeared. Generally, however, the patient was not completely free from discomfort in the period elapsing between the two sets of symptoms. A mild cough, slight nausea, or a headache were often present at this stage. Complete freedom from symptoms seems to have existed only in cases 12 and 16. In case 3 there was no such interval, and it was also practically absent in some of the other cases.

It is not possible to base any conclusion regarding the severity of the later symptoms on the strength of the initial symptoms. In case 2, for instance, the first stage was extremely mild but severe pulmonary edema subsequently developed, while as regards patient 6, who had violent discomfort in the beginning, the subsequent course was fairly uneventful. Nor does the presence or absence of a latent interval appear to affect the later course of the illness. In case 3 the patient was not definitely symptom-free at any stage, and in case 12 there were no symptoms at all after the first stage of discomfort had subsided, but in both instances a fatal pulmonary edema developed in the later stage.

The duration of the free interval, in the cases in which it could in some measure be distinguished, was 3 to 6 hours.

Among the later symptoms a cough and breathing difficulties are the most pronounced. The cough is extremely irritating, and prevents the patient from sleeping. The severity of the shortness of breath varies, but in many cases it can be intense. Not infrequently there are pains in the chest, especially behind the sternum. A high degree of weakness is usually present. Nausea and

The sedimentation rate is normal in the early stage of the poisoning. There may later be a moderate rise.

Electrocardiographic changes have been demonstrated by Ahlberg and Dahlberg (10) in one case, and they were also noted in one of the cases in the present series (case 3, immediately before death). In the cases mentioned in the literature there are only a few references to the electrocardiographic aspect, and the two instances mentioned above seem to be the only ones which have displayed abnormality. In the case reported by Ahlberg and Dahlberg the tracings soon became normal again. As regards my patients, nos. 2, 4, 8, 11, 12, 13 & 15 yielded a normal electrocardiogram; thus even when the poisoning was extremely severe no abnormality was apparent. In both the cases showing an irregular mechanism the changes consisted in a depression of the S—T interval, except for that in lead I, and in a shortening of the auriculo-ventricular conduction time; the latter sign has been interpreted as an indication of myocardial damage (Söderström, 11). It would seem, therefore, that even the severe forms do not as a rule cause any changes in the electrocardiogram. Of the two patients yielding abnormal tracings, the one survived and the other died. It does not seem possible, therefore, to make any prognosis on the basis of the electrocardiographic findings.

Can these clinical signs and symptoms be said to coincide with the observations in proved nitrous gas poisoning?

Nitrous gas poisoning is by no means a rare occurrence. Schultz-Brauns (12), in 1930, reviewed no less than 150 deaths and »innumerable» cases of illness. A fair amount is therefore known about the syndrome, despite the fact that the number of cases submitted to thorough clinical examination is not large as yet (Ahlberg and Dahlberg, 10). Flury (13) has classified the condition into four different types with varying clinical symptoms. In the *irritant gas type* there first occur signs of local irritation, then a latent period of a few hours, and finally pulmonary edema followed by death within 1 to 2 days. In the *reversible type* there appear within rapid succession of one another dyspnea, cyanosis, vomiting, vertigo, and sometimes unconsciousness. If the person affected can be removed at once from the poisonous atmosphere he soon makes a complete recovery. In the *shock type* there appear almost instantaneously signs of suffocation, convulsions, and cessation of

the breathing. This form only occurs when high concentrations of the gas are suddenly inhaled into the lungs. In the *combined type* there are immediate cerebral symptoms which subside after the affected person is removed from the poisoned air, but after a latent period lasting a few hours breathing difficulties and other signs of pulmonary edema appear. The reason why the picture varies to such an extent in the different cases is thought by Flury to be due not only to different concentrations of the gases but also to variations in the composition of the nitrous fumes. When a high concentration of nitric monoxide is present the cerebral signs are predominant, while nitric dioxide exercises a more local irritant action and tends to cause pulmonary edema.

The clinical observations both in my series and in the cases reported in the literature in which the poisoning had arisen under similar circumstances are in good agreement with the description worked up by Flury. On the other hand, they do not tally in the least with the syndrome occurring in poisoning due to carbon monoxide, arsenuretted hydrogen, or phosphoretted hydrogen, substances to which the poisoning in these cases has been ascribed. The syndrome bears the closest resemblance to that caused by phosgene, although in the latter the initial symptoms do not appear in the same way.

3. *The roentgenographic appearances in the lungs.*¹ In six of the cases described, the roentgen examination revealed lesions in the lungs. In most of the cases in which the roentgenograms showed no positive changes the examination had been carried out so many days after the actual accident that, judging from the experiences gained from the other cases, there had been time for even established lesions to disappear. In the one case in which examination was possible at the initial stage the roentgen picture of the lungs was normal despite the fact that there were definite signs of irritation of the respiratory passages.

Thus, in all severe cases, roentgenologic signs of pulmonary lesions are in all probability one of the distinctive features in the secondary stage.

In the severe cases, confluent areas of increased density are

¹ In the preparation of the section on the roentgenographic appearances valuable assistance has been given by Dr. C. J. Hansson, of the Roentgen Diagnostic Department at the Söhlgren Hospital, Gothenburg.

visualized. In the milder forms, or at the convalescent stage, scattered mottling is to be seen. The diseased patches are scattered all over the pulmonary fields but are most numerous in the middle zone of the lungs. This distribution in the pulmonary field is so typical that the very fact of its presence on the roentgen film is almost sufficient to justify a diagnosis.

In the cases in which mottling is visualized the films sometimes bear a striking resemblance to those produced in miliary tuberculosis, especially if, as in cases 2 and 5, there are at the same time signs of an old tuberculosis. However, the typical distribution in the pulmonary field, with the densest concentration of the lesions in the middle zone, differs from the appearances usually seen in miliary tuberculosis.

It is surprising how pronounced these pulmonary lesions may appear in patients with only slight or no demonstrable physical symptoms from the lungs and a good general condition (cf. cases 5 and 9).

The changes are in some patients extremely transient, as in cases 2, 4, and 9, while in others they persist for several weeks before disappearing entirely. In one instance (case 8), after receding in some measure, they increased again in extent.

Lesions of this kind have previously been reported in only three cases, namely by Ziemke (14), Renander (15), and Ahlberg and Dahlberg (16). They tally with the observations in connection with nitrous gas poisoning occurring under different conditions (cf. Ahlberg and Dahlberg's publication).

Whether similar syndromes may be produced by other types of gas poisoning causing toxic pulmonary edema is not yet clear, since roentgen examinations of the lungs do not appear to have been carried out in such cases.

The changes may recur (as in case 8) in established nitrous gas poisoning also. Dr. E. Åkerberg, of the Alingsås Hospital, has sent the writer a report on such a case.

4. *Can permanent sequelae result from the poisoning?* Of the cases reported in this paper there was only one, no. 8, in which there were permanent sequelae. Ever since the accident the patient has suffered from rather troublesome shortness of breath after exertion. Patient 2, who suffered from severe headaches and fatigue after the accident, has since then been subject to long periods

of weakness and nervousity; however, as he had been treated for the same trouble even before the mishap the poisoning can hardly be blamed for these symptoms.

It is difficult to form any idea from the literature of the extent to which permanent sequelae may result. Although cases of this form of poisoning are fairly common they have as a rule only aroused interest, and been described, after a death has occurred, and there are thus no detailed reports including the milder forms also. A few cases with lasting after-effects have been published, however. Floret (16) has described a patient who suffered for a long time from nervousness, tremor, tachycardia, and arrhythmia of the heart. Jacobi (17) mentions a case in which, in his opinion, previously existing myocardial damage was aggravated by poisoning resulting from work with acetylene flames. Bulmer, Rothwell, and Frankish (18) made a report on a patient who had breathing difficulties on exertion for a long while after the mishap. Among the cases reviewed by Schiötz (3), patient 2 suffered from dyspnea for a long period, and no. 5 was left with permanent shortness of breath and a tendency to cough. Judging both from the writer's series, and the literature, therefore, permanent sequelae seem to be rare.

In nitrous gas poisoning brought about in other ways, it is also known that permanent after-effects may follow, in the form of a cough lasting over a long period, breathing difficulties, heart trouble, and a reduction in weight. (Cf. Floret, 19.) Symptoms of this kind are said to be very common.

5. *Patho-anatomic observations.* The most pronounced changes are found in the lungs and in the brain, but other organs may also be affected.

As regards the lungs, even the gross appearance in the four postmortems appended displayed an advanced edema, in some places combined with small foci of pneumonia. Under the microscope, most of the alveoli were seen to be filled with edema of great acuteness. In some areas the effusion was mixed with an abundance of leukocytes, with the result that small patches of bronchopneumonia had been formed. The alveoli not filled by edema were distended to their maximum size and some had damaged walls. In addition to leukocytes, the alveoli also contained desquamated epithelium. Some of these epithelial cells had several nuclei. In the bronchi purulent bronchitis was usually present. In case 15,

however, despite the advanced changes in the alveoli, the bronchi showed no lesions. Inflammatory degeneration was also noted in the trachea, but this varied in severity in the different cases.

In all the reports on patients who died under similar circumstances, a high degree of pulmonary edema is mentioned in connection with the macroscopic appearance observed at the postmortem (Hulst, 20; Holtzmann, 21; Kissinger, 22; Haegele, 23; Walz, 24; Ziemke, 14; Bridge, 25; Küster, 26; Maenicke, 5; Nordmann, 27; Mawick, 8; Crämer, 28; Wright-Smith, 29). In the cases in which a histologic examination was carried out (Hulst, Holtzmann, Haegele, Ziemke, Walz, Küster, Nordmann, Wright-Smith) edema in an advanced stage was also found, in some instances accompanied with inflammation; thus, the same findings as in my series. On the other hand, as far as I can find, no other publication contains reference to the occurrence of multinuclear epithelial cells in the alveoli.

Thus, the most severe lesions are to be found in the alveoli and in the finer bronchial branches, while the upper respiratory passages are involved to a much lesser degree. The changes can therefore not be ascribed to the direct corrosive action of the poisonous fumes.

Effusion into the pleura may occur (see the autopsy report in case 14, the clinical and roentgenographic findings in case 8, and Hulst's paper, 20).

Examination of the brain reveals in some cases, in addition to hyperemia, small hemorrhages with a characteristic tendency to be situated in the white matter. Hemorrhages of this kind were present in large numbers in case 3, and sparsely in case 14. They were not present in cases 12 and 15. The older bleedings are of the nature of ring hemorrhages. Necrosis of the central vessel in the hemorrhage is often observed. The endothelium in the fine cerebral vessels is swollen. The ganglion cells, on the other hand, show no definite changes.

Brain purpura in patients who have died after using acetylene flames has previously been mentioned by Hulst (20), Holtzmann (21), Haegele (23), Walz (24), Ziemke (14), and Wright-Smith (29). As the brain does not appear to have been examined in most of the other cases submitted to autopsy, it would seem that small hemorrhages in the brain is a common finding. The typical concentra-

tion of these lesions in the white matter is stressed by Hulst (20), Haegele (23), Ziemke (14), and other investigators. The latter also found in his case symmetrical degeneration of the lenticular nucleus. This feature was also observed by Holtzmann (21).

In two cases in the present series the heart showed changes, in the form of small subendocardial hemorrhages (cases 14 and 15). Similar hemorrhages are also mentioned in connection with one of Maenieke's (5) cases. Enlargement of the heart has been described by Kissinger (22), and Ahlberg and Dahlberg (10) also observed the same feature in their clinical examinations. Walz (24) and Haegele (23) both noted fatty degeneration of the heart muscle.

As regards the alimentary canal, punctate hemorrhages were seen in the mucous membrane of the stomach in case 14. Ziemke (14) found a severe necrosis in the rectum, in his case.

Walz (24) reported fatty degeneration of the liver, and Wright-Smith (29) toxic lesions in the liver, the kidneys, and the spleen.

How do these changes tally with the observations in proved nitrous gas poisoning?

The above-mentioned lesions in the lungs and in other parts of the respiratory tract are in complete agreement with the features described by Schultz-Brauns (12) as being characteristic of nitrous gas poisoning. The multinuclear epithelial cells in the alveoli are also mentioned in his publication.

The changes found in the brain in connection with this form of poisoning also correspond in the different publications (Schultz-Brauns, 12; Winblad, 30). The numerous small hemorrhages in the white matter occur in both groups of cases. In nitrous gas poisoning arising under circumstances other than from welding with acetylene, however, hemorrhages in the brain have never been observed in patients dying less than 37 hours after the accident (Winblad, 30), and it is thought, therefore, that the occurrence or non-occurrence of the hemorrhages must be dependent on the time elapsing between the accident and the death of the patient (Schultz-Brauns). This is not absolutely in agreement with the observations made in poisoning incurred from the use of acetylene flames. In case 14 in my series, petechial hemorrhages were present despite the fact that the time between the poisoning and the death of the patient could certainly not have exceeded 23 hours. Cerebral hemorrhages were also observed in the cases reported by Hulst

(20) and by Wright-Smith (29). In these, an interval of 24 hours had elapsed between the mishap and death. On the other hand, in my case 12, in which death occurred 36 hours after the accident, and case 15, in which 40 hours passed before the patient expired, there were no definitely established cerebral hemorrhages. Thus, although the time is not the only factor determining the occurrence of the bleedings, yet it would seem that hemorrhages in the brain do not arise at the time of the accident but rather one or two days later.

The changes observed in the other organs as a result of acetylene gas welding are essentially the same as those occurring in established nitrous gas poisoning (Schultz-Brauns, 12). A certain interest is attached to the fact that Loeschke (31) noted lobar pneumonia in a patient who died seven days after the accident. Crämer (28) also, basing his arguments on experimental investigations, came to the conclusion that lobar pneumonia may quite well arise as a sequel to nitrous gas poisoning. Thus, although no case of this kind has as yet been reported in connection with acetylene welding, yet such a possibility cannot be left out of account. Further, it is of interest to note that obliterating bronchiolitis and carnifying miliary bronchopneumonia have been observed in cases of nitrous gas poisoning in which death occurred some time after the accident. This provides an explanation of the shortness of breath and the cough which sometimes persist as lasting sequelae. The changes in other organs satisfactorily explain other permanent after-effects.

Do similar syndromes arise under other circumstances?

Both Schultz-Brauns (12) and Winblad (30) have drawn attention to the complete conformity existing between the anatomic findings in poisoning produced by certain war gases, in particular phosgene and chloropicrin, and those brought about by nitrous fumes. On the other hand, the syndrome in the latter is quite different from that seen in carbon monoxide poisoning; this is all the more remarkable since many authors (Hulst, 20; Holtzmann, 21; Haegeler, 23; Ziemke, 14) have diagnosed CO intoxication precisely on account of the anatomic findings. The pulmonary lesions are in no way similar to those occurring in CO poisoning. Cerebral hemorrhages certainly may occur in the latter form of poisoning, but when present they are located in the gray matter as well, espe-

cially in the central ganglia [Weimann, (32)], and are not concentrated exclusively in the white matter as was so consistently the case with the patients who died as a result of acetylene gas welding. Ziemke's (14) assertion, that isolated cases of CO poisoning may present a similar picture, is no doubt correct [Weimann, (32)], but it is hardly likely that this form of poisoning would produce in all such cases a set of symptoms so strikingly different from those commonly occurring in CO poisoning.

Influenza combined with hemorrhagic bronchopneumonia and brain purpura may also cause a somewhat similar syndrome, but in such cases the lesions are of a more definitely inflammatory nature. For details in this connection, the reader is referred to Schultz-Brauns (12).

Both the clinical and the roentgenographic findings and the patho-anatomic appearances are thus in complete accordance with the observations in proved cases of nitrous gas poisoning. Among other forms of poisoning, it is only a few types caused by gases used in warfare that bear any definite resemblance to the variety under discussion, but in these the clinical signs and symptoms show certain divergences, and the conditions necessary for the evolving of phosgene did not exist when the various accidents occurred.

It must therefore be regarded as established that the poisoning occurring in connection with acetylene welding in a confined space is due to the evolving of nitrous fumes. (Possibly also, fumes arising from the piece of work in hand may sometimes be a contributory cause.)

6. *Treatment.* When a person begins to feel discomfort while manipulating an acetylene flame in a confined space the first measure is to see that he is removed from the poisonous atmosphere.

From the experiences gained in connection with phosgene poisoning, which is very similar, it is well known that the patient must have complete rest after being exposed to the dangerous gas, even though all the symptoms may have rapidly subsided. The case reports appended in the present paper point in the same direction. In case 12, in which the initial symptoms were violent, no secondary symptoms appeared, while many of the other patients who had only slight discomfort to begin with, later became seriously ill. Only the first-mentioned patient had complete rest.

If secondary symptoms develop, complete rest is still of vital

importance. For the cough, various types of remedial medicine may be given, and for the threatening cardiac insufficiency, cardiac stimulants. As may be seen from the present series, immediate relief is often produced by oxygen therapy and by bloodletting. To counteract the tendency towards the development of pulmonary edema, the injection of calcium salts (Ahlberg and Dahlberg, 10) has been suggested, but caution ought undoubtedly to be exercised in using such a thrombosis-promoting agent in an illness so likely to be complicated by thrombosis (see Schultz-Brauns, 12). In some cases I have used injections of hypertonic glucose solutions, and I consider this treatment to be of value.

The length of time the patient is kept in bed must depend on the symptoms in the individual cases. If pulmonary lesions have been visualized on the roentgenogram, they ought to have completely disappeared before the patient is allowed to get up. Not even then can the possibility of a recurrence be totally excluded. (See Åkerberg's case, page 26.)

7. *Hygienic precautions and prophylaxis.* It is evident both from the appended case reports, and from numerous statements in the literature, that work involving the use of acetylene flames is often carried out under such conditions that nitrous gases in dangerous concentrations are evolved without any effective protective measures having been taken to counteract them. Neither the employers nor the workmen have been aware of the risk. Enlightenment on this aspect of the work is essential. In all probability it will be necessary to issue special instructions for the use of these flames, as has been done in Germany (see Schiötz, 1).

Because of insufficient knowledge regarding the symptoms and the risks involved, the men often go on working in the poisoned air even after they have begun to experience severe discomfort. Information concerning the necessity of breaking off the work and of getting complete rest, if symptoms arise during welding with acetylene gas in confined spaces, should be widely broadcast among all workmen engaged in this type of work.

What are the external circumstances necessitating special protective measures?

Rimarski and Konschak (4) consider that if the room is well-ventilated and its volume over 100 cubic metres, there is no danger of nitrous gas poisoning. Among the cases described in this paper,

however, there was one in which poisoning resulting in death was incurred while work was in progress in a space having a volume of 770 cubic metres (case 14). In cases 8 to 10 the work was being done in a room of 150 cubic metres. It is clear, therefore, that a severe form of poisoning may also arise in rooms of fairly large volume. And obviously, the smaller the space, and the longer the work is continued, the greater will be the risk.

It stands to reason, as is proved by the evidence of both my series and the investigations of Rimarski and Konsehak, that in case of spaces having a volume of less than 100 cubic metres, air conveyed to the room merely by means of a compressed air tube is insufficient to ensure satisfactory ventilation. In such cases it is essential that the poisonous fumes be drawn out by a suction apparatus situated as near as possible to the place of work and that fresh air be simultaneously pumped into the room. When it is a question of very confined spaces either a gas-mask provided with a filter to deal with sour gases, or a respirator or oxygen inhaler should be used. The two last-mentioned apparatuses have been in use during the past year at one of the shipbuilding yards in Gothenburg at which accidents had previously occurred, and they have won the unqualified approval of the employees.

Summary.

Sixteen cases of poisoning of varying degrees of severity, occurring during welding with acetylene gas, are described. Four of the patients died, and the postmortem records relative to these cases are presented.

In every instance the poisoning is believed to have resulted from the inhalation of nitrous fumes evolved in the flame. In three of the cases acrolein may have been a contributory cause.

The clinical picture is described in detail and the question of permanent sequelae is discussed. Characteristic lesions were observed in many of the roentgen films of the lungs. A description of the anatomic changes is given. Both the clinical and the anatomic findings agree well with the changes observed in proved nitrous gas poisoning.

The method of treatment, hygienic precautions, and the prophylactic aspect are also discussed.

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Nouvelle classification des cardiopathies congénitales.

Par

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(Ce travail est parvenu à la rédaction le 6 Mars 1944).

A. Introduction.

Diverses classifications des cardiopathies congénitales ont été proposées au cours de ces vingt dernières années. L'une d'entre elles, due à Dry, est basée sur des données embryologiques. Sont successivement envisagées: 1° les malformations associées au développement du septum; 2° les anomalies résultant de troubles dans l'évolution du bulbe cardiaque; 3° les malformations liées au développement des arcs aortiques; 4° les anomalies des artères coronaires; 5° la dextrocardie.

Maud Abbott, dont la contribution à l'étude des cardiopathies congénitales a été extrêmement importante, surtout en ce qui concerne l'anatomo-pathologie, a proposé une classification adoptée à l'heure actuelle par la très grande majorité des auteurs. Cette classification distingue un groupe d'affections sans signification clinique et un groupe d'affections ayant une signification clinique. Dans la première catégorie elle range, d'une part, les anomalies qui n'entraînent aucun trouble circulatoire, comme, par exemple, la dextrocardie, et d'autre part, les monstruosité incompatibles avec la vie, telles que, notamment, l'acardie et l'ectopie cardiaque cervicale. Elle divise la seconde catégorie en trois groupes:

1° Un groupe acyanotique qui comprend les malformations n'entraînant pas de communication entre les cavités cardiaques (valvule aortique bicuspide, sténose aortique, coarctation de l'aorte, arc aortique droit, anomalies péricardiques, etc.).

2° Un groupe de malformations, où il existe en principe un «shunt» artério-veineux et où la cyanose manque habituellement, mais où elle peut apparaître d'une façon transitoire ou terminale; ce groupe renferme notamment les anomalies du septum interauriculaire, les anomalies du septum interventriculaire et la persistance du canal artériel.

3° Un groupe cyanotique, subdivisé lui-même en cardiopathies à cyanose modérée, cyanose marquée et cyanose extrême et comprenant entre autres malformations la sténose pulmonaire, la tétralogie de Fallot, le complexe d'Eisenmenger, la transposition des grands vaisseaux de la base.

B. Critique de la classification de Maud Abbott.

La classification de Maud Abbott constitue une tentative remarquable de synthèse des affections congénitales du cœur. Elle est pourtant susceptible de diverses critiques.

Tout d'abord la distinction entre malformations à signification clinique et malformations sans signification clinique nous paraît mal établie. Le groupe dit sans signification clinique comprend en effet, d'une part, des anomalies relevant uniquement du domaine de la tératologie et, d'autre part, des malformations comme la dextrocardie dont le diagnostic précis présente une réelle utilité dans la pratique courante.

Par ailleurs, la classification de l'auteur est essentiellement basée sur la présence ou l'absence de cyanose. Ce symptôme présente évidemment un grand intérêt pour le clinicien, mais il nous paraît impossible de nous en servir pour étayer une classification. L'origine de la cyanose est fréquemment complexe en effet et n'est pas nécessairement liée à l'existence d'une malformation cardiaque. On sait qu'elle apparaît lorsque le taux d'hémoglobine réduite du sang capillaire dépasse 5 g pour 100 cm³. Rappelons quels sont les facteurs susceptibles d'entraîner l'apparition d'un excès d'hémoglobine réduite dans le sang capillaire:

1° *Une hématoze défœctueuse au niveau du réseau pulmonaire.* Le sang peut quitter les pœumons avec une charge trop faible en oxygène et présenter par conséquent une insaturation élevée. C'est ce que l'on observe au cours de la pneumonie ou dans les affections pulmonaires chroniques (emphysème, bronchite chronique, etc.).

2° *Une désaturation excessive du sang par ralentissement circulatoire.* L'insuffisance cardiaque s'accompagne d'un ralentissement circulatoire parfois considérable. La stase périphérique qui en résulte, entraînant une désoxygénation exagérée, détermine l'apparition d'un excès d'hémoglobine réduite dans le sang capillaire.

Des phénomènes identiques pourront s'observer dans des stases périphériques localisées, indépendantes de toute affection cardiaque; c'est ce qu'on note au cours des acrocyanoses.

3° *Un «shunt» veino-artériel.* La pénétration dans le sang artériel d'une certaine quantité de sang veineux entraîne la présence d'un excès d'hémoglobine réduite dans le sang capillaire.

4° *Une augmentation du taux de l'hémoglobine totale.* Au cours des polyglobulies, quelle qu'en soit l'origine, le taux d'hémoglobine réduite est augmenté proportionnellement au taux d'hémoglobine totale.

Divers facteurs sont par conséquent susceptibles de produire la cyanose. Une classification des cardiopathies congénitales, basée sur l'existence ou l'absence de ce symptôme, nous paraît donc peu justifiée. Quelques remarques au sujet des groupes envisagés par Maud Abbott nous permettront de préciser cette affirmation.

Cet auteur distingue tout d'abord un groupe *acyanotique* dans lequel elle range les malformations n'entraînant pas de communication entre les cavités cardiaques.

L'absence de «shunt» n'exclut pourtant pas nécessairement la cyanose et les anomalies rangées dans ce groupe pourront parfaitement s'accompagner d'une teinte bleuâtre des téguments, si d'autres facteurs que le «shunt» interviennent pour la produire. C'est ainsi par exemple que la coarctation de l'aorte, arrivée à la période d'insuffisance circulatoire, présente parfois un degré marqué de cyanose.

Maud Abbott envisage ensuite un groupe de cardiopathies congénitales ne s'accompagnant pas en principe de cyanose, mais où ce symptôme peut apparaître d'une façon transitoire ou terminale

(*maladie de Roger et canal artériel, par exemple*) Chez de tels sujets, l'apparition de la cyanose serait due, pour elle, au renversement d'un «shunt» normalement artério-veineux. Cette manière de voir nous paraît hypothétique.

Chez l'enfant porteur d'une communication interventriculaire et qui présente un accès de cyanose transitoire (cyanose paroxysmique de Variot), on admet trop facilement que, sous l'influence de la toux ou d'un effort à glotte fermée, la pression augmente brusquement dans le cœur droit et détermine un renversement du «shunt». Ce mécanisme d'apparition de la cyanose n'est pas impossible, mais on peut, avec une égale vraisemblance, invoquer un trouble de l'hématose pulmonaire consécutive à l'asphyxie.

De même, on admet qu'au cours d'une broncho-pneumonie ou d'une insuffisance cardiaque terminale, il se produit un renversement du «shunt» (cyanose terminale de Bard et Curtillet). Il est tout aussi plausible de penser que, chez de tels sujets, la cyanose résulte d'une hématose pulmonaire insuffisante en cas de broncho-pneumonie et est consécutive au ralentissement circulatoire lors d'une insuffisance cardiaque.

Maud Abbott considère enfin un groupe cyanotique subdivisé lui-même en cardiopathies à cyanose modérée, cyanose marquée et cyanose extrême et où sont rangés entre autres la sténose pulmonaire, la tétralogie de Fallot et le complexe d'Eisenmenger.

En réalité, la cyanose peut être présente dans ces affections, mais ce symptôme est loin d'être constant. Dans la sténose pulmonaire, la cyanose est relativement rare; quand elle existe, elle est due à un ralentissement circulatoire excessif.

Dans la tétrade de Fallot, et le complexe d'Eisenmenger, la cyanose est, pour Maud Abbott, consécutive au «shunt» veino-artériel. Cependant un «shunt» veino-artériel n'implique pas nécessairement l'existence d'une cyanose. Le taux d'hémoglobine réduite ne dépasse guère chez l'homme normal 3 g pour 100 cm³. Comme la cyanose n'apparaît que pour un taux d'hémoglobine réduite atteignant 5 g pour 100, il faut donc, en l'absence d'autres facteurs, que le «shunt» veino-artériel soit suffisant pour ajouter 2 g d'hémoglobine réduite aux 3 g existant normalement au niveau des capillaires. Pour qu'une telle éventualité se produise, il est nécessaire, d'après Lundsgaard et Van Slyke, que le sang veineux «shunté» atteigne une valeur d'environ 38 %. Si le «shunt» est

moindre et si, répétons-le, aucun autre facteur n'intervient, la cyanose pourra être totalement absente. Ainsi s'expliquent les cas de tétralogie de Fallot sans cyanose rapportés dans la littérature (Fleury). L'absence ou la présence de cyanose ne permettent donc pas de nier ou d'affirmer l'existence d'un «shunt» veino-artériel.

Il résulte de ces remarques qu'une anomalie qui, d'après la classification de Maud Abbott, devrait être acyanotique, pourra parfaitement présenter de la cyanose et qu'une autre, rangée par cet auteur dans le groupe cyanotique, pourra en être exempte.

C. Mise en évidence des «shunts».

L'aspect clinique et le pronostic d'une affection congénitale du cœur dépendent essentiellement de l'existence, de la direction et de l'importance d'un «shunt» mettant en communication les cavités cardiaques. Il est par conséquent du plus grand intérêt de pouvoir mettre en évidence la présence d'un «shunt» artério-veineux ou celle d'un «shunt» veino-artériel.

1. «Shunt» artério-veineux.

On peut supposer, a priori, que certaines malformations du cœur s'accompagneront de la pénétration de sang artériel dans le sang veineux. En effet, durant toute la révolution cardiaque, la pression est toujours plus élevée dans le cœur gauche que dans le cœur droit. Par conséquent lors de l'existence d'une communication interauriculaire isolée ou d'une communication interventriculaire simple ou encore d'une communication aortico-pulmonaire, il est à présumer que le sang veineux sera partiellement artérialisé.

L'un de nous, avec P. Govaerts, a montré qu'il était relativement aisé de prouver la réalité de ce «shunt». Si au cours d'une communication interventriculaire, par exemple, le sang du ventricule droit est partiellement artérialisé, il en résulte que sa teneur en acide carbonique est moindre que celle du sang d'un ventricule droit normal. La mise en évidence d'une teneur en acide carbonique anormalement basse dans le sang du cœur droit permettra donc d'affirmer l'existence d'un «shunt» artério-veineux. La méthode directe pour arriver à ce but consisterait à ponctionner le ventri-

cule droit. Bien que cette technique ait été parfois utilisée chez l'homme au cours de ces dernières années, elle paraît devoir rester exceptionnelle. L'application du procédé de Plesch permet d'évaluer la teneur en CO_2 du sang du ventricule droit par une méthode indirecte. Supposons, en effet, que nous puissions plonger dans le sang de l'artère pulmonaire une très petite bulle d'air. Un équilibre va s'établir en quelques instants entre l'atmosphère de la bulle et les gaz du sang; à ce moment la pression partielle de CO_2 à l'intérieur de la bulle sera précisément telle qu'à son contact le sang veineux ne perd ni ne gagne d'acide carbonique. Reportée sur la courbe de dissociation des bicarbonates sanguins, cette pression partielle indiquera combien de volumes pour cent de CO_2 le sang renferme. Ce raisonnement est valable si au lieu d'une bulle on considère un volume gazeux beaucoup plus grand, à condition que le contact s'établisse avec une grande masse de sang. L'équilibre sera atteint avec une aisance particulière si, dans le volume gazeux mis en contact avec le sang, on a établi d'avance une pression partielle d'acide carbonique voisine de celle que l'on suppose exister dans le sang veineux.

C'est ce que l'on réalise dans la méthode des «rebreathings» de Plesch, rendue pratique par Henderson et Prince. Dans ce procédé, c'est tout le contenu des voies aériennes qui joue le rôle de la bulle de gaz. Le sujet inhale le contenu d'un sac renfermant de l'air mélangé d'environ 5 % d'acide carbonique. Il rejette ensuite dans le sac l'air qui a été pendant quelques instants au contact des capillaires pulmonaires. L'opération est répétée un certain nombre de fois et, ainsi, dans le mélange gazeux qui a été successivement inhalé et expiré, la pression partielle du CO_2 devient constante. Cet équilibre est défini par le fait que le sang provenant du cœur droit ne perd ni ne gagne plus de CO_2 au contact de l'atmosphère réinhalée; à ce moment la pression partielle de ce gaz correspond exactement, sur la courbe de dissociation, à la teneur en CO_2 du sang veineux oxygéné. Par cet artifice, on est parvenu à faire jouer à tout le contenu des voies aériennes le rôle d'un aérotonomètre.

L'étude d'un grand nombre de sujets témoins nous a montré que chez eux le sang veineux de l'artère pulmonaire (sang veineux mêlé) s'équilibre avec un mélange gazeux renfermant 6.54 % de CO_2 en moyenne, ce qui correspond à une pression partielle de

45.96 mm de mercure. Cette valeur s'obtient en multipliant le taux d'acide carbonique observé au moment où l'équilibre est obtenu, par la pression barométrique du moment diminuée de la tension de vapeur d'eau régnant dans l'arbre pulmonaire (47 mm Hg).

Chez quatre sujets porteurs d'une communication interventriculaire simple, nous avons trouvé que le sang veineux mêlé s'équilibrait avec une pression partielle d'acide carbonique plus faible que chez l'individu normal. En effet, ces quatre cas de maladie de Roger nous ont fourni des chiffres de 5.55, 5.32, 5.74 et 5.84 % de CO_2 soit 39.26, 38.39, 39.54 et 41.95 mm de mercure. C'est le résultat que l'on devait prévoir si, du fait de la communication interventriculaire, le sang veineux est mélangé à une certaine quantité de sang artériel provenant du ventricule gauche.

L'étude d'un patient porteur d'une communication aortico-pulmonaire nous a donné des résultats similaires. Chez ce sujet, le sang de l'artère pulmonaire s'équilibrait avec un mélange gazeux renfermant 5.85 % de CO_2 , ce qui correspondait à une pression partielle de 41.24 mm de mercure.

L'existence d'un «shunt» artério-veineux dans certaines cardiopathies congénitales est donc démontrable.

2. «Shunt» veino-artériel.

Il peut exister des malformations congénitales où le «shunt» sera veino-artériel.

Une telle éventualité se rencontrera lors de la coexistence d'une communication interventriculaire et d'une sténose de l'artère pulmonaire. Dans une pareille association, l'obstacle au courant sanguin déterminé par le rétrécissement de l'artère pulmonaire, entraîne un accroissement considérable de la pression dans le ventricule droit et détermine par là un «shunt» veino-artériel. La pénétration de sang veineux dans le sang artériel se produira également dans certains cas de naissance anormale de l'aorte: il peut arriver que celle-ci chevauche les deux ventricules et reçoive du sang provenant de ces deux cavités.

Un «shunt» veino-artériel peut être mis en évidence à l'aide de certaines techniques que nous allons exposer brièvement.

Les résultats les plus précis sont obtenus en déterminant la composition gazométrique des sangs artériels et veineux. Voici les

données recueillies chez un de nos patients porteur d'une tétralogie de Fallot avec cyanose et leur interprétation.

Oxygène consommé par minute	197 cm ³
Métabolisme	+ 12
Air alvéolaire	5.28 vol% de CO ₂
Capacité du sang en oxygène	22.53 vol%
Taux d'oxygène du sang artériel	19.17 vol%
Taux d'oxygène du sang veineux	11.51 vol%
Différence artério-veineuse en oxygène ..	8.14 vol%

Insaturation artérielle en oxygène (sang de l'artère fémorale):

$$22.53 \text{ vol. \%} - 19.17 \text{ vol. \%} = 3.36 \text{ vol. \%}$$

Insaturation veineuse en oxygène:

$$22.53 \text{ vol \%} - 11.51 \text{ vol. \%} = 11.02 \text{ vol. \%}$$

Insaturation capillaire en oxygène:

$$\frac{3.36 + 11.02}{2} = 7.19 \text{ vol. \%}$$

Taux d'hémoglobine réduite du sang capillaire:

$$7.19 \times 750 = 5.39 \text{ g \%}$$

Il s'agit d'un patient n'ayant aucun trouble de l'hématose au niveau des poumons et dont l'air alvéolaire présente une composition normale. Or l'insaturation artérielle en oxygène du sang prélevé dans l'artère fémorale est de 3.36 vol.%; en d'autres termes, le sang de l'artère fémorale n'est saturé qu'à 85 %, alors que chez l'individu normal ce taux atteint 90 à 98%. Cette insaturation artérielle ne peut s'expliquer que par la pénétration anormale d'une certaine quantité de sang veineux dans l'arbre artériel. L'existence d'un «shunt» est ainsi démontrée.

On s'est efforcé à diverses reprises de déterminer d'une façon approximative l'importance du «shunt» veino-artériel (Lundsgaard et Van Slyke, Dautrebande, Marschall et Meakins, Segall, Richards, Cossio et Berconsky). La formule la plus simple permettant d'obtenir ce «shunt» est due à Lundsgaard et Van Slyke; elle s'exprime de la façon suivante:

$$a = \frac{A - IT}{V - IT}$$

Dans cette formule:

α = «shunt» veino artériel

T = taux d'hémoglobine totale du sang (c'est à dire la capacité multipliée par 750 millig.)

A = taux d'hémoglobine réduite du sang artériel (c'est à dire l'insaturation artérielle en oxygène multipliée par 750 millig.)

V = taux d'hémoglobine réduite du sang veineux (c'est à dire l'insaturation veineuse en oxygène multipliée par 750 millig.).

I = fraction de l'hémoglobine totale passant sous forme réduite au niveau du poulmon (chez le patient présentant une hématoze pulmonaire normale, la moyenne de sa valeur est de 0.05).

Appliquée à notre malade, cette formule nous a donné les résultats suivants:

$$\alpha = \frac{2.52 - (0.05 \times 16.90)}{8.26 - (0.05 \times 16.90)} = 0.23.$$

En d'autres termes 23 % du sang veineux passent dans le coeur gauche sans traverser les poulmons.

Chez notre malade, la différence artério-veineuse en oxygène atteint 8.14 vol.%, traduisant ainsi une désaturation excessive du sang au niveau des capillaires. Cette désaturation est en rapport avec le ralentissement circulatoire consécutif à la polyglobulie et selon toute vraisemblance à un certain degré d'insuffisance cardiaque. La cyanose de cette malade a par conséquent une origine mixte. Le «shunt», à lui seul, serait insuffisant pour la déterminer.

Nous donnons, ci-après, les résultats obtenus par les mêmes techniques chez un patient porteur d'une cardiopathie congénitale complexe: dilatation de l'artère pulmonaire, petite aorte, hypertrophie du coeur droit, communication interauriculaire, communication interventriculaire. (Lequime, Van Heerswyngheles et Herlant):

Oxygène consommé par minute	218 cm ³
Métabolisme	+ 17
Air alvéolaire	5.13 vol. % de CO ₂
Capacité du sang en oxygène	31.80 vol. %
Taux d'oxygène du sang artériel	23.40 vol. %
Taux d'oxygène du sang veineux	11.86 vol. %
Différence artério-veineuse en oxygène	..	11.54 vol. %

Insaturation artérielle en oxygène (sang de l'artère fémorale):

$$31.8 \text{ vol. \%} - 23.40 \text{ vol. \%} = 8.40 \text{ vol. \%}$$

Insaturation veineuse en oxygène:

$$31.8 \text{ vol. \%} - 11.86 \text{ vol. \%} = 19.94 \text{ vol. \%}$$

Insaturation capillaire en oxygène:

$$\frac{19.94 + 8.40}{2} = 14.17 \text{ vol. \%}$$

Taux d'hémoglobine réduite du sang capillaire:

$$14.17 \times 750 = 10.63 \text{ g\%}$$

Le sang artériel prélevé au niveau de l'artère fémorale présente une insaturation en oxygène de 8.40 vol. %; en d'autres termes, ce sang n'est saturé qu'à 74 %. Etant donné qu'il n'existe chez cette malade aucun trouble de l'hématose, l'insaturation résulte nécessairement de la pénétration dans le cœur gauche d'une certaine quantité de sang veineux.

La formule de Lundsgaard et Van Slyke, appliquée à ce cas, donne les résultats suivants:

$$\alpha = \frac{630 - (0.05 \times 23.85)}{14.95 - (0.05 \times 23.85)} = 0.37$$

Il existe par conséquent chez ce patient un «shunt» veino-artériel atteignant 37 %.

Au cours de ces dernières années, on a proposé d'appliquer les méthodes de détermination de la vitesse circulatoire à la mise en évidence d'un «shunt» veino-artériel (Pijoan et Bérard, Mac Guire et Goldman, Lian). Le cyanure de sodium et les substances sapides ont été utilisées. En présence d'un temps circulatoire très fortement raccourci, on est en droit de penser à l'existence d'un «shunt» veino-artériel.

Un temps circulatoire normal n'exclut pas nécessairement, cependant, l'existence d'un «shunt» veino-artériel. Il peut arriver en effet que ce dernier existe, mais soit trop faible pour permettre à la substance utilisée de parvenir avec une concentration suffisante au niveau du sinus carotidien ou au niveau de la langue. D'autre part, le raccourcissement dû à un «shunt» important pourra être éventuellement masqué par une stase périphérique accentuée.

Nous sommes par conséquent en possession de méthodes précises permettant la mise en évidence des «shunts» artério-veineux et veino-artériel.

D. Classification des cardiopathies congénitales.

Nous avons rappelé précédemment que l'aspect clinique et le pronostic d'une cardiopathie congénitale étaient essentiellement dominés par l'existence, la direction et l'importance d'un «shunt» mettant en communication les cavités cardiaques. C'est ainsi par exemple que des patients ayant un «shunt» artério-veineux ne présenteront pas en principe de trouble de l'hématose et toléreront leur cardiopathie d'une manière satisfaisante.

L'application des techniques de détermination des «shunts» permet d'établir une classification des cardiopathies congénitales du coeur rendant parfaitement compte des aspects physiopathologiques présentés par ces anomalies.

1° Cardiopathies congénitales ne s'accompagnant pas d'un «shunt» entre les systèmes artériels et veineux.

Dextrocardie.

Diverticule du péricarde.

Anomalies de l'arc aortique.

Sténoses aortiques

Coarctation de l'aorte.

Sténoses de l'artère pulmonaire.

Dilatation primitive de l'artère pulmonaire sans malformation septale ¹.

Affections plus rares: ectopie cardiaque, aplasie péricardique, hypertrophie congénitale idiopathique, anomalies des valvules auriculo-ventriculaires et semi-lunaires, transposition totale des

¹ Malformation complexe bien individualisée à la suite des travaux de Laubry et de ses collaborateurs; elle est caractérisée par une dilatation très importante de l'artère pulmonaire, une hypoplasie de l'aorte et un développement considérable du coeur droit. Cette cardiopathie congénitale s'accompagne souvent d'une communication interauriculaire (Laubry et Routier), plus rarement d'une communication interventriculaire (Lequime, Van Heerswyngheles, et Herlant). La coexistence d'une malformation septale détermine l'apparition d'un «shunt» qui est veino-artériel par suite de l'hypertrophie considérable de la musculature du coeur droit.

gros vaisseaux, anomalies des artères coronaires ou des veines pulmonaires, acardie.

2° *Cardiopathies congénitales s'accompagnant d'un «shunt» entre les systèmes artériel et veineux.*

a) *«Shunt» artério-veineux.*

Communication interventriculaire

Persistance du canal artériel

Communication interauriculaire simple (persistance du trou de Botal)¹.

Affections plus rares: anévrysme congénital du sinus de Valsalva avec anomalie du septum aortique, transposition des gros vaisseaux avec défaut du septum interventriculaire.

b) *«Shunt» veino-artériel.*

Tétralogie de Fallot.

Complexe d'Eisenmenger.

Dilatation primitive de l'artère pulmonaire avec malformation septale.

Affections plus rares: coeur biventriculaire triloculaire, coeur biauriculaire triloculaire, coeur biloculaire.

E. Conclusions.

La classification des maladies congénitales du coeur, proposée par Maud Abbott, a été adoptée par la très grande majorité des auteurs. Elle est essentiellement basée sur la présence ou l'absence de cyanose dans les diverses malformations.

Une telle classification est loin de répondre à la généralité des faits observés. La cyanose est en effet un phénomène dont l'origine est souvent complexe; elle n'est pas nécessairement liée à l'existence d'une anomalie cardiaque définie.

¹ Cette malformation ne donne lieu à aucune symptomatologie clinique et constitue une trouvaille d'autopsie; aucun document gazométrique n'a donc pu être recueilli. Il est cependant à présumer qu'une telle cardiopathie s'accompagne d'un «shunt» artério-veineux, pour autant que la communication soit fonctionnelle. Les embolies croisées, parfois signalées dans les persistances du trou de Botal, ne peuvent évidemment s'expliquer que par un renversement temporaire de la direction du «shunt». Il convient d'ailleurs d'insister sur le fait que ces embolies croisées sont infiniment plus rares qu'on ne le dit classiquement. Leur diagnostic doit toujours s'accompagner de grandes réserves.

Le tableau clinique d'une cardiopathie congénitale est dominé par l'existence, la direction et l'importance d'un «shunt» mettant en communication les cavités cardiaques. Il nous paraît donc primordial de pouvoir mettre en évidence la présence d'un «shunt» et d'en préciser la direction et l'importance.

Lors d'un «shunt» artério-veineux, le sang du coeur droit est partiellement artérialisé. Dans ces conditions, si l'on fait faire au patient des «rebreathings» à partir d'un mélange d'air et d'acide carbonique, on voit que le sang veineux de l'artère pulmonaire s'équilibre avec une pression partielle d'acide carbonique plus faible que chez l'individu normal.

La mise en évidence d'un «shunt» veino-artériel peut être réalisée par l'étude de la composition en oxygène des sangs artériel et veineux. En l'absence de modifications de l'hématose pulmonaire, l'existence d'une insaturation en oxygène du sang artériel dépassant les chiffres normaux, démontre la pénétration d'une certaine quantité de sang veineux dans le système artériel. Une formule due à Lundsgaard et Van Slyke permet de déterminer d'une façon approximative l'importance de ce «shunt» veinoartériel.

Un raccourcissement notable de la vitesse circulatoire est également un argument intéressant en faveur de l'existence d'un tel «shunt».

La connaissance précise de ces notions de «shunt» artério-veineux et de «shunt» veino-artériel permet une classification rationnelle des cardiopathies congénitales. Celle-ci s'établira de la façon suivante:

1° Cardiopathies congénitales ne s'accompagnant pas de «shunt» entre les systèmes artériel et veineux.

2° Cardiopathies congénitales s'accompagnant d'un «shunt» entre les systèmes artériel et veineux.

a) «Shunt» artério-veineux

b) «Shunt» veino-artériel.

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REVUE DES LIVRES.

Esben Kirk, Klinik und Behandlung der Azidose mit isotonischer Natriumbikarbonatlösung. Für praktische Ärzte und Krankenhausärzte. Price: Dan. Kr. 18: —. Einar Munksgaard, Copenhagen. Johann Ambrosius Barth, Leipzig. 1944.

In recent times the acidosis-alkalosis problem has attracted considerable interest within Scandinavian medical circles. Thus it was the main topic at the combined annual meeting of Swedish internists and surgeons in the autumn of 1943. One of the pioneers of the alkali therapy in Scandinavia is the author of this work, who was probably the first in this part of the world to begin a systematic treatment of the acidotic condition with isotonic sodium bicarbonate on American lines.

Thus, the author has special qualifications for his work, which — in a Danish edition — has previously been highly appreciated by his Scandinavian colleagues. When he now addresses an international circle of readers in a German edition, it is with full justification. Probably there exists no concise and clear survey of relevant questions comparable with the present survey by Kirk. The author addresses himself to practising doctors and to hospital doctors. In the first place, however, it is probably a question of a treatment which falls to the lot of the hospital doctor. The presentation is so attractive, however, and deals with such important questions, that the practising doctor also should find it profitable, even though it will perhaps be only in exceptional cases that he will need to put the information in the book to practical use. In an introductory chapter the author gives a brief historical survey of the treatment of acidosis with alkalis, which covers a period of about 100 years. What is presented here in concise form is later dealt with more in detail under the special chapter-headings,

a procedure which has the advantage of affording a good survey and giving concreteness to the presentation.

The author is a zealous champion of the isotonic sodium bicarbonate therapy and with every justification, as excellent results can be shown. However, he is very moderate, and the presentation is characterized by critical clearness throughout, as for instance in the description of the treatment of diabetic coma. In this connection the author utters a warning against an all too unrestricted use of sodium bicarbonate, owing to the risk of alkalosis; and he points out the decisive importance of insulin for a good result. At the same time he is not afraid to state definitely, for instance, that in severe cases up to 2 litres of sodium bicarbonate can be given without risk. Even if his scheme of treatment for diabetes coma must be taken rather as an example of a procedure, which must be modified all according to the nature of the case, than as a hard and fast treatment, it is instructive and, used intelligently, should be of great use.

The work is illustrated by a number of well chosen morbid histories, which increases the value of the book. The last chapter on the technique in the determination of the bicarbonate content of the plasma must be considered superfluous in this book. Where this investigation can be carried out, detailed description of Van Slyke's method is already available. Some small details show that the work is a translation, in that mention is made of conditions prevailing in Denmark which do not exist outside a small circle. This will certainly be corrected in a new English edition, which may be expected within the near future.

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Studies on the influence of magnetism on the oxygen absorption in man.

By

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Copenhagen.

(Submitted for publication February 14, 1944).

In a previous paper (*Acta med. Scandinav.*, 97: 341, 1938) I have discussed the presumably soothing and sedative effect of magnetism in acute inflammatory conditions and in chronic joint lesions. In the latter cases the soothing effect was probably the more important, even though the results were found subsequently to last a considerable length of time. The cessation of pain is valid as a proof, however, only to him who has the pain, and it takes many testimonies to make the serviceability of the remedy convincing in general. No single physician would be able to collect such a material. I have tried, therefore, in some other way to prove objectively whether magnetism has any demonstrable effect on the animal organism — *in casu*, man.

A priori, only two facts suggest themselves for this purpose, namely, the capacity of magnetism for action on iron and the iron content of the human organism. The action of magnetism on iron being an atomic effect, the form of the iron in the organism should make no difference. Considering the function of the iron in the body, the question arises whether it might not be practicable to establish some difference in the oxygen absorption with or without exposure of the body to the action of a strong magnet. It was this idea that led to the experiments which will be described in the

following — even though any direct influence of the magnetism upon the oxygen absorption appears improbable.

The experiments were carried out in the Medical Department B of the Rigshospital, Copenhagen, and the experimental technique has been the regimen adopted by the hospital for the usual clinical determination of the rate of metabolism. The experimental conditions were far from ideal, but for practical reasons it was not possible to realize some planned improvements. The room in which the tests take place is next to a corridor the floor of which is covered with linotol which by no means is sound-muffling, and the possibility of traffic and noise in this corridor while determination of the metabolism is going on is continually present — occurring often indeed. As there is only one room for this examination, up to 5 persons may be lying here at the same time. The disturbing influence of this condition is cut down somewhat by the continuous presence of a watch, also during the resting period, but it cannot be completely avoided that restlessness of one patient is transmitted to the others. It is further necessary to wheel the metabolism apparatus from one patient to another — which also involves some noise. As many determinations are carried out almost daily and as the assistants change rather often it is not to be wondered at if errors in the care of the apparatus happen rather frequently.

Nevertheless the experiments were taken up under the present conditions because the possible disturbing influences might be expected to appear as accidental and thus not efface the evidence of a sufficiently strong systematic factor if any such would turn up, or at any rate not give rise to such a factor — even though these disturbances may be assumed to blur the picture somewhat.

The metabolism apparatus here employed is Krogh's spirometer (*Wien klin. Wchnschr.* 35: 290, 1922). This apparatus was not manufactured in Krogh's workshop, however, and the valves which fit but loosely in the sockets and have to be put in place at each test appear less reliable than the ones furnished by Krogh's workshop. Instead of water, mineral oil was used in the apparatus. The periods were determined by means of a stop watch. The percentages of metabolism are calculated after the Benedict-Harris standard. Patients staying in the above-mentioned department were the experimental subjects, and no selection of

the subjects was made. They were all used for the experiments or for control in the order in which they were sent from the department to the metabolism room for the clinical examination within the given period. Only for a short period were the patients sent to the metabolism room for the sake of this experiment; and among these patients, too, no selection was made — they were taken in the order in which they came.

The patients had not been placed on any particular diet prior to the experiment, and they were all fasting since their preceding supper. They were all wheeled in their beds to the metabolism room, where they stayed in bed during the experiment and also through the preliminary resting period, which lasted for at least half an hour.

In the following the term »experimental subjects» means persons exposed to magnetism during the determination of the rate of metabolism, the current being connected with an electromagnet standing alongside, with one pole fairly perpendicular on the skin, but at a certain distance from the skin. »Controls» means persons going through the same procedure of determination of metabolism but without exposure to the magnetism.

One of the electromagnets mentioned in the previous paper was placed at the head of the bed, at the commencement of the resting period, alongside the head of the controls as well as the experimental subjects. In the case of experimental subjects care was taken to place the surface of the pole about 3 cm from the head of the subject (left parietal or temporal bone). The magnet was placed in this location merely because this was found to be the most practical, and some preliminary experiments had not shown that it made any difference which part of the body was directly exposed to the magnet. The south pole of the magnet was employed in every instance.

In the first series of the experiments the magnet was not set up for the controls, but this made no difference in the outcome as compared to the three subsequent series of controls. As only three magnets were employed, it became necessary when more than three patients were placed in the room to move the magnet after completion of the first experiment, over to the next subject; but the second experiment was not performed till the magnet had been standing for at least half an hour alongside the subject.

The heads of the beds were turned in the same direction and the electrical switches with which the magnets were connected were situated on the wall back of the heads of the beds, so that the patients could not see them; and we took care that the patients did not hear when we connected the current with the magnets.

For all the patients, experimental subjects as well as controls, the procedure now was as follows: The subjects were directed to breathe in the spirometer, and when 8 minutes had gone in this way the time was marked on the drum by lifting the writer for a moment; simultaneously, another person connected the current with the electromagnet of the experimental subjects, while all the patients — experimental subjects and controls — kept breathing in the spirometer for additional 5 minutes.

After the end of the experiment each spirometer tracing was treated as two curves, the first covering 8 minutes, the second 5 minutes.

The idea of the experiment was then to see whether there might be any noticeable difference between the absorption of oxygen per minute in the first and second parts of the curve, and whether the experimental subjects presented some difference in this respect that could not be found in the curves for the controls.

A total of 208 patients were used as experimental subjects and controls. Of this total, 115 showed a standard metabolism of 110 % or less, while 93 had a standard metabolism over 110 %.

Altogether 559 metabolism curves were obtained for the experimental subjects and controls. Of this total, 264 were experimental curves, 132 of which showed a standard metabolism of 110 % or less and 132 showed a standard metabolism exceeding 110 %.

Of the total 295 control curves, 130 showed a metabolism of 110 % or less, while 165 showed a metabolism over 110 %.

Some of the patients served both as experimental subjects and controls while others were employed only as one or the other. Among the patients presenting a considerable increase in the standard metabolism, exophthalmic-goiter was the most frequent disease; a few of these patients had leukemia, and one was suffering from cancer.

For some of the exophthalmic-goiter patients curves of the standard metabolism were obtained also after thyroidectomy; and hence these patients are recorded both under curves showing

increase in metabolism and under curves with no increase in the metabolism. Something similar applies also to some other patients but as a rule they were individuals showing a rate of metabolism round the upper normal limit and thus happening sometimes to reach a few per cent over this level, sometimes to fall a little lower.

The experimental subjects or controls who showed a standard metabolism under 110 % were not infrequently diagnosed as myxoedematous; but otherwise they were sorts of patients such as are encountered in a medical department among those in whom it may be desirable to determine the rate of metabolism. The age of the patients varied between 15 and 80 years, but only one patient belonged to the age-class of 70—80 years, being 77 years old.

When no further details are given about these patients, it is because the material is not large enough by a detailed description of the individual subjects to throw any additional light on the question here concerned.

Of the curves obtained, here I have taken into account all those in which a straight line could be drawn through the expiratory apices for a reasonable length of the curve after the curve had started in a certain direction. Far from all the curves were ideal; still it would seem rather objectionable to be all too strict in one's requirements concerning the form of the curves if we were to observe the general impression desired, as the faculty of obtaining beautiful curves appears to be something individual.

As mentioned, each curve was treated like two curves, covering respectively a period of 8 and 5 minutes. The oxygen consumed in the latter period in cm^3 per min. was subtracted from the oxygen absorbed in the first period, and the difference was expressed in percentage of the amount consumed in the first period (Tables 1 and 2). With a view to the error in the drawing of the line, which was always done by the same person however, a difference of plus or minus 2 % is reckoned as 0.

The results are recorded in 4 series, which were limited merely by accidental discontinuance of the examinations.

A priori it was to be expected that several of the curves would keep about the same direction through all 13 minutes. Others were expected to show an increase in the oxygen consumption in

Table 1.

Persons with Standard Metabolism Equal to or Less than 110 %. Difference in Oxygen Absorption between the First and Last Parts of the Curve.

Controls			Experimental subjects		
Unchanged %	Lowered %	Increased %	Unchanged %	Lowered %	Increased %
Autumn 1942					
0	4	7	0	7	18
0	5	5	0	4	9
0	23	6	0	<u>2</u>	5
0	6	3	0		6
0	6	8	0		8
0	3	8	0		5
0	3	17	0		8
0	11	8	0		7
0	4	6	0		10
0	4	3	0		4
0	20	6	0		8
0	4	6	0		6
0	8	3	0		10
0	6	<u>13</u>	<u>0</u>		4
<u>14</u>	<u>5</u>		<u>13</u>		3
	15				8
					23
					3
					<u>10</u>
					19
42 curves			34 curves		
December 1942					
0	5	4	0		9
0	5	13	0		8
0	6	14	0		6
<u>3</u>	17	3	0		<u>3</u>
	8	6	0		
	5	13	<u>0</u>		
	3	5	5		
	9	5			
	6	5			
	6	<u>9</u>			
	8				
	6				
	<u>12</u>				
24 curves			8 curves		

(Table 1. cont.)

Controls			Experimental subjects		
Unchanged %	Lowered %	Increased %	Unchanged %	Lowered %	Increased %
February 1943					
0	9	4	0	4	4
0	5	5	0	7	8
0	5	3	0	12	12
0	22	<u>3</u>	0	11	3
0	6	3	0	4	7
0	5		0	4	30
<u>0</u>	3		0	3	12
6	4		0	3	18
	<u>8</u>		<u>0</u>	11	23
			8	8	5
				5	3
				7	6
				4	4
				5	6
				5	8
				<u>5</u>	<u>3</u>
				16	16
17 curves			40 curves		
Spring 1943					
0	11	10	0	5	4
0	11	14	0	10	3
0	9	4	0	4	10
0	3	3	0	3	3
0	3	7	0	9	8
0	5	4	0	3	4
0	11	7	0	26	9
0	16	9	0	3	8
0	8	3	0	10	5
0	5	4	0	8	9
0	3	7	0	12	10
0	7	3	0	4	4
0	8	4	0	<u>6</u>	5
0	10	<u>5</u>	0	13	12
0	9	14	0		10
<u>0</u>	13		0		3
16	<u>6</u>		<u>0</u>		11
	17		17		5
					36
					<u>8</u>
					20
47 curves			50 curves		

Table 2.

Persons with Standard Metabolism Greater than 110 %. Difference in Oxygen Absorption between the First and Last Parts of the Curve.

Controls.			Experimental subjects.		
Unchanged %	Lowered %	Increased %	Unchanged %	Lowered %	Increased %
Autumn 1942					
0	12	3	0	10	8
0	3	5	0	5	10
0	10	12	0	5	5
0	4	3	0	13	4
0	6	14	0	20	4
0	5	8	0	15	
0	6	6	0	3	
0	9	5	0	6	
0	4	30	0	5	
0	6	3	0	24	
0	3	6	0	4	
0	9	11	0	13	
0	13	11	0	16	
0	3	6	0	9	
0	5	16	14	3	
0	7	4		15	
0	16	4			
17		4			
		11			
		19			
52 curves			33 curves		
December 1942					
0	17	4	0	6	8
0	23	7	0	16	3
0	3	10	0	33	9
0	10	7	0	10	14
0	4	7	4	4	6
0	4	17			9
0	20	13			6
0	13	12			
8	13	6			
	6	11			
	3	4			
	11	3			
		10			
		4			
		18			
		10			
		11			
		10			

Table 3.

Persons with Standard Metabolism \leq 110 %.

Controls	Experimental subjects
<p><i>Autumn 1942: 42 curves</i></p> <p>Unchanged 14 = 33 % Lowered 15 = 36 % Increased 13 = 34 %</p> <p><i>December 1942: 24 curves</i></p> <p>Unchanged 3 = 12 % Lowered 12 = 50 % Increased 9 = 38 %</p> <p><i>February 1943: 17 curves</i></p> <p>Unchanged 6 = 35 % Lowered 8 = 47 % Increased 3 = 18 %</p> <p><i>Spring 1943: 47 curves</i></p> <p>Unchanged 16 = 34 % Lowered 17 = 36 % Increased 14 = 30 %</p> <p><i>Total: 130 curves</i></p> <p>Unchanged 39 = 30 % Lowered 52 = 40 % Increased 39 = 30 %</p>	<p><i>Autumn 1942: 34 curves</i></p> <p>Unchanged 13 = 38 % Lowered 2 = 6 % Increased 19 = 56 %</p> <p><i>December 1942: 8 curves</i></p> <p>Unchanged 5 = 63 % Lowered 0 = 0 % Increased 3 = 37 %</p> <p><i>February 1943: 40 curves</i></p> <p>Unchanged 8 = 20 % Lowered 16 = 40 % Increased 16 = 40 %</p> <p><i>Spring 1943: 50 curves</i></p> <p>Unchanged 17 = 34 % Lowered 13 = 26 % Increased 20 = 40 %</p> <p><i>Total: 132 curves</i></p> <p>Unchanged 43 = 33 % Lowered 31 = 23 % Increased 58 = 44 %</p>

the latter part of the curve — something that is said to take place if the patient tires and hence becomes somewhat restless or even spasmodic, or at the sound of a sudden noise, a not infrequent phenomenon in these quarters — which may produce involuntary muscular contractions.

Finally, the oxygen consumption may be expected to fall in the latter part of the curve if the experimental subject has been restless at the commencement of the examination and becomes quiescent gradually. For such a reaction is to be expected the first time the examinee is subjected to determination of his metabolism; and perhaps it is to be expected also in the nervous exophthalmic goiter patients.

The curves for the experimental subjects and for the controls were then assorted in 0, plus and minus groups, depending on

Table 4.
Persons with Standard Metabolism > 110 %.

Controls		Experiment subjects	
Autumn 1942: 52 curves		Autumn 1942: 33 curves	
Unchanged	17 = 33 %	Unchanged	14 = 42 %
Lowered	16 = 31 %	Lowered	15 = 45 %
Increased	19 = 36 %	Increased	4 = 13 %
December 1942: 37 curves		December 1942: 14 curves	
Unchanged	8 = 22 %	Unchanged	4 = 29 %
Lowered	11 = 30 %	Lowered	4 = 29 %
Increased	18 = 48 %	Increased	6 = 42 %
February 1943: 16 curves		February 1943: 32 curves	
Unchanged	5 = 31 %	Unchanged	11 = 34 %
Lowered	7 = 44 %	Lowered	11 = 34 %
Increased	4 = 25 %	Increased	10 = 32 %
Spring 1943: 60 curves		Spring 1943: 53 curves	
Unchanged	27 = 45 %	Unchanged	24 = 45 %
Lowered	15 = 25 %	Lowered	20 = 38 %
Increased	18 = 30 %	Increased	9 = 17 %
Total: 165 curves		Total: 132 curves	
Unchanged	57 = 34 %	Unchanged	53 = 40 %
Lowered	49 = 30 %	Lowered	50 = 38 %
Increased	59 = 36 %	Increased	29 = 22 %

whether the last 5 min. of the determination of the metabolism showed an unchanged, increased or lowered oxygen absorption. For the estimation of a possible difference in the groups, the number of curves in each group is first counted and calculated in percentage of the total number, and the percentages obtained for the experimental subjects are compared with those obtained for the controls. The results of this are recorded in Tables 3 and 4, the total number of curves from all 4 examination periods being recorded at the bottom of the tables.

Considering first the results obtained from all the individuals with a rate of metabolism equal to or lower than 110 % (Table 3), it will be noticed that respectively 33 % and 30 % showed no difference in the oxygen consumption during the first and last part of the examination. Turning to the individuals showing a rise or

fall in the oxygen consumption, on the other hand, we find a difference in the two groups. The controls show a decrease in the oxygen consumption in 40 % of the curves, and an increased oxygen consumption in 30 % of the curves, whereas the experimental subjects show a decrease in the oxygen consumption in 23 %, and a rise in 44 %. A similar difference is found for the curves obtained in the individual periods if only the number of experiments is fairly large.

The difference presented by these two groups may be summed up as follows: the curves representing exposure to magnetism show a greater percentage of subjects with increased oxygen absorption in the last 5 min. of the experiment than do the curves representing the controls, and also a smaller number with a decrease in the oxygen absorption in the same periods.

Turning then to experiments on persons with a standard metabolism over 110 % — in particular the totals recorded at the bottom of Table 4 — we find for the controls an almost equal percental distribution of the cases over unchanged, lowered and increased oxygen absorption, even though the number of curves with lowered oxygen absorption is smaller than the other two categories; and the same result is obtained for the individual examination periods provided they include a fair number of cases.

As to the curves for the experimental subjects in Table 4, the numbers of curves with unchanged and decreased oxygen absorption are almost equal percentally, whereas the number of curves with increased oxygen absorption is considerably lower; and the same is found for two of the individual examination periods.

In this group of individuals, then, we find the difference to be as follows: the percental frequency of a decreased oxygen absorption is higher for the experimental subjects than for the controls, whereas the frequency of a rise in the oxygen absorption is lower in the experimental subjects.

On comparison of the groups with increased metabolism with those showing a normal or subnormal metabolism, it will be noticed that the differences between the experimental subjects and the controls go in opposite directions. The groups with a normal rate of metabolism show a tendency to an increase in the oxygen absorption when the electromagnet is active, whereas the persons with increased metabolism show a tendency to a fall in the oxygen ab-

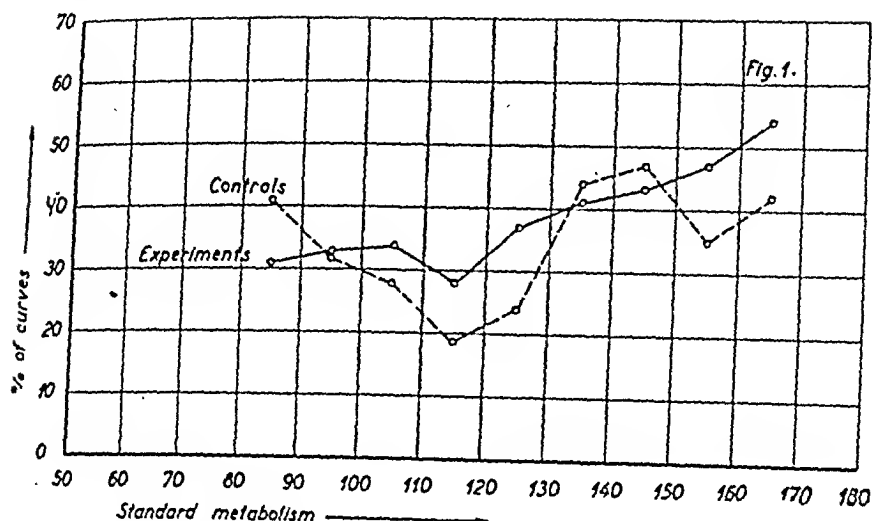


Fig. 1. Percental distribution of the numbers of curves showing an unchanged oxygen consumption in the latter part of the curve at the various rates of metabolism.

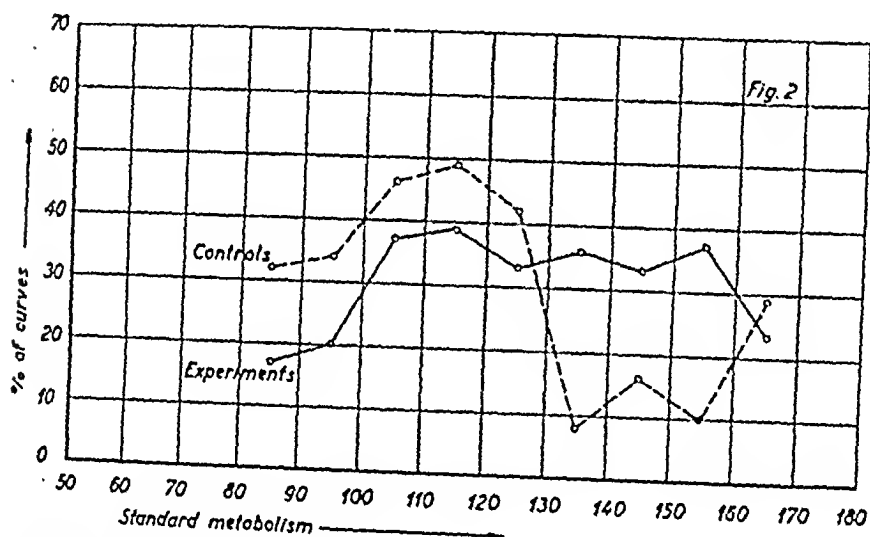


Fig. 2. Percental distribution of the numbers of curves showing a lowered oxygen consumption in the latter part of the curve at the various rates of metabolism.

sorption under the same experimental conditions. In the ordinary determinations of the metabolism, without the current being connected with the magnet — *i. e.*, the controls — the individuals with a normal metabolism show a tendency to a decrease in the oxygen absorption, whereas individuals with increased metabolism show a tendency to an increase in the oxygen absorption.

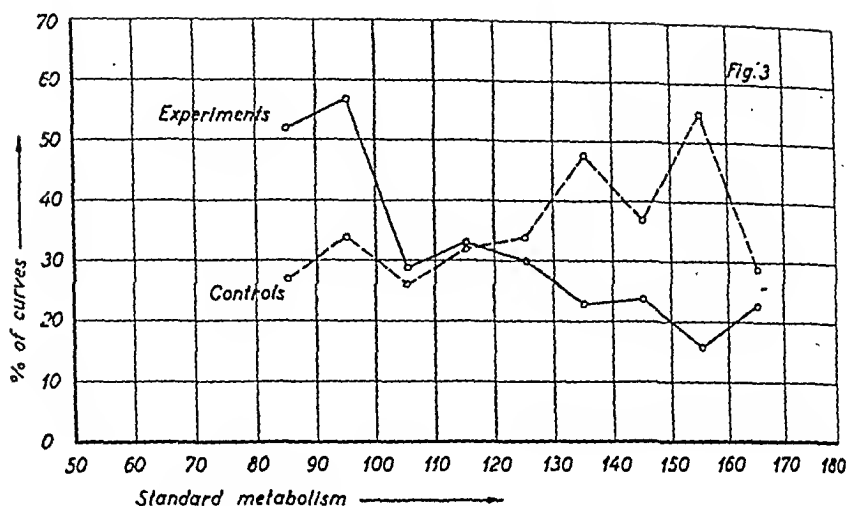


Fig. 3. Percental distribution of the numbers of curves showing an increased oxygen consumption in the latter part of the curve at the various rates of metabolism.

The cause of these differences will not be discussed here in detail. It seems only natural, however, that the nervous exophthalmic-goiter patients more readily become restless under the determination of the metabolism than do the less nervous individuals with a normal rate of metabolism. On the other hand, it seems strange that the same does not hold true when the magnet is in function.

The curves in Figs. 1, 2 and 3, corresponding to Table 5, illustrate the distribution of the percental numbers of the control and experimental curves at the different levels of the rate of metabolism. In Figs. 2 and 3 it will be noticed that the curves in which «something happens» are groups mostly round the extreme rates of metabolism, whereas the numbers with plus or minus for the oxygen absorption become alike towards the transition between normal and pathological. So, the result obtained by these examinations should depend on the starting material, *i. e.* on the standard metabolism of the person examined.

If, for instance, a material had been selected in which the standard metabolism fell about at the level where the numbers of experimental and control curves cross each other — *i. e.* at the level where the same number of each kind shows a rise or a fall in the oxygen consumption — the result would show that nothing took place under the influence of the magnet, and the whole thing

Table 5.

No. of Curves within the Various Rates of Standard Metabolism with, respectively, Unchanged, Lowered and Increased Oxygen Absorption in the Latter Part of the Curve.

Controls $\approx 110\%$								Experimental subjects $\approx 110\%$							
Standard metabolism %	No	0	—	+	% 0	% —	% +	Standard metabolism %	No	0	—	+	% 0	% —	% +
50—60	0							50—60	1			1			
60—70	1		1					60—70	3		1	2			
70—80	1		1					70—80	9	3	1	5	33	11	55
80—90	22	9	7	6	41	32	27	80—90	29	9	5	15	31	17	52
90—100	47	15	16	16	32	34	34	90—100	54	18	11	25	33	20	57
100—110	58	16	27	15	28	46	26	100—110	35	12	13	10	34	37	29
110—120	31	6	15	10	19	49	32	110—120	18	5	7	6	28	39	33
120—130	33	8	14	11	24	42	34	120—130	27	10	9	8	37	33	30
130—140	27	12	2	13	44	8	48	130—140	22	9	8	5	41	36	23
140—150	19	9	3	7	47	16	37	140—150	21	9	7	5	43	33	24
150—160	20	7	2	11	35	10	55	150—160	19	9	7	3	47	37	16
160—170	17	7	5	5	42	29	29	160—170	13	7	3	3	54	23	23
170—180	9	5	3	1	56	33	11	170—180	7	4	2	1	57	29	14
180—190	5	0	4	1	0	80	20	180—190	1	0	1	0			
								190—200	2	0	2	0			
								200—210	1		1				

would not involve any problem. Now, however, with the actual examinations as here presented, we still have to investigate whether the observed differences are real or merely accidental.

It would not seem reasonable to base this investigation merely on the number of curves of the various categories. To me it seems more rational also to take into account the magnitude of the oxygen consumption found for each curve — the more so as «unchanged» really very well may signify a positive or definite change in the result. If, for instance, we imagine that the magnet actually exerts some influence in this respect, so that a given result without the magnet, say, would have been an increase in oxygen consumption, while with the magnet the result turned out as an unchanged oxygen absorption, the «unchanged» result actually means a change. The figures for the magnitude of the changes in the metabolism observed in the individual curves are recorded in Tables 1 and 2.

This material was presented before Mr. Helge Petersen¹, Director of the Danish Meteorological Institute, Copenhagen, who has been kind enough to appraise this material statistically as follows:

The present numerical material is conceived in this way, that when a metabolism curve is divided into two parts, the first and the last part, and when the rate of the metabolism is measured for the two parts separately, we may assume that as far as regards a large number of «equal» individuals the possible *changes* in the metabolism from the first part of the curve to the last part will be distributed approximately «normally» round an average value, which is characteristic of the «equal» individuals concerned. If this change in the rate of metabolism from the beginning to the end of the curve may be determined with a sufficiently small mean error, it will be possible to demonstrate whether some influence acting on the individuals during the tracing of the latter part of the curve has brought about a change in the metabolic rate other than that which may occur in the absence of the influence mentioned, namely: if the mean errors for the two changes are essentially smaller than the difference between the numerical values for the two changes. For in that case the mean error of the difference will also be essentially smaller than the difference itself.

The material consists of four experimental series, each of which comprising one set of metabolism curves *without* any influence of foreign factors (designated as «untreated») and one set of curves (designated as «treated»), during the latter part of which the individuals were exposed to the influence of another factor. For each set of curves we calculate the average value (\bar{M}) of the *changes* (differences) in the oxygen consumption from the first to the last part of the curve.

Owing to the rather wide dispersion of the figures in proportion to the number of measurements, we lump the figures in groups of four units. Assuming «no change» to cover the changes within the interval from +2 to -2 (uncertainty of measuring), we lump the changes 3, 4, 5 and 6 into one group, to which we assign the average change of 4.5; and 7, 8, 9 and 10 are lumped into the group of 8.5, and so on. The material may then be recorded as shown in Table 6.

¹ I wish to acknowledge my indebtedness to Director Helge Petersen for the following statistical treatment and appraisal of my numerical material.

Table 6.

Statistical Treatment of the Material.

Untreated		Treated	
Metabolism ≤ 110	Metabolism > 110	Metabolism ≤ 110	Metabolism > 110
<i>Autumn 1942.</i>			
M Cases -0.7 ± 1.1 (42)	M Cases $+1.2 \pm 1.0$ (52)	M Cases $+4.2 \pm 1.0$ (34)	M Cases -3.4 ± 1.3 (33)
<i>December 1942.</i>			
-0.6 ± 1.5 (24)	$+1.3 \pm 1.6$ (37)	—	-1.1 ± 3 (14)
<i>February 1943.</i>			
-2.6 ± 1.5 (17)	-0.7 ± 1.5 (16)	$+1.4 \pm 1.3$ (40)	-1.9 ± 1.4 (32)
<i>Spring 1943.</i>			
-1.1 ± 1.0 (47)	$+0.4 \pm 0.9$ (60)	$+1.4 \pm 1.2$ (50)	-1.5 ± 0.8 (53)

In Table 6 the mean error is too large to allow of any definite numerical values being established for M. Still, it is quite conspicuous that a change of signs takes place from «untreated» to «treated», and that this change of signs for individuals with a metabolism of ≤ 110 is the opposite of the change of signs for individuals with a metabolism of > 110 .

Table 7.

Statistical Treatment of the Material.

Untreated		Treated	
Metabolism ≤ 110	Metabolism > 110	Metabolism ≤ 110	Metabolism > 110
Cases -1.1 ± 0.6 (130)	Cases $+0.7 \pm 0.6$ (165)	Cases $+2.3 \pm 0.7$ (132)	Cases -2.1 ± 0.7 (132)

The values obtained for M differ in each category generally so little that it may be reasonable to lump all four series into one group in order to try to determine M with greater certainty. The result is given in Table 7.

Corresponding to the increased number of observations the mean error has now become so small that the values recorded

for M may be taken with some probability as *approximate* measures for the average change in the oxygen consumption from the first to the last part of the curves. It seems unquestionable that this change goes in the opposite direction for individuals with a metabolic rate under, respectively over, 110 % and for »treated», respectively »untreated» individuals.

Calculating the differences for »treated» minus »untreated», we have:

Metabolism

≤ 110

$+ 3.4 \pm 0.9$

Metabolism

> 110

-2.8 ± 0.9

where the changes during the treatment make their appearance with a mean error of 25—30 % only.

The difference between the effects of the treatment of individuals with a metabolic rate of ≤ 110 % and of individuals with a metabolic rate of > 110 % is found to be

$+ 6.2 \pm 1.3$.

Besides the above-mentioned four experimental series, there are three additional series of experiments in which »controls» are lacking, *i. e.*, series in which no determination of metabolism was carried out on corresponding »untreated» patients. The results obtained in these series were as follows:

- A. 22 fasting individuals, given a preliminary diet, showed an average *increase* in the rate of metabolism during the treatment, amounting to $M = + 6.3 \pm 1.1$.
- B. 12 fasting individuals showed on an average $M = + 4.6 \pm 1.5$.
- C. 20 experiments on *one person*, fasting, gave $M = + 1.8 \pm 0.6$.

All the individuals in these three series had a rate of metabolism of 110 % or less.

These experiments give qualitatively the same result as the above-mentioned series. But it is a striking fact that they all show a considerably smaller relative mean error than do the main experiments. This may conceivably be due to a greater *uniformity* of the experimental material in these series (preliminary diet, one person). This may perhaps suggest that the uncertainty

in the main experiments in part is associated with a certain degree of heterogeneity in the patient material.

(Signed Helge Petersen.)

When, in conclusion, we are to discuss whether magnetism has proved to have any influence on the oxygen absorption in man, it has to be established primarily that a systematic influence on this process was observed with a rather high degree of probability, and that this probability — as shown by the figures — is further supported by the fact that the effect on the two categories of metabolism (increased and non-increased) goes in opposite directions — even in this surprising manner, that the oxygen absorption has a tendency to fall in the nervous exophthalmic-goiter patients, whereas it increases in the «normal» subjects. Generally an extraneous factor may be expected to be able only to increase the metabolism, and it would seem reasonable if this effect turned out to be strongest in the most nervous individuals — as was observed indeed in the control curves obtained from the patients in whom the rate of metabolism was increased.

The question then arises: Will it be reasonable to assume that this probable effect is due to the magnetism?

To this the answer naturally will be that, as far as it has been possible to ascertain, magnetism or no magnetism constitutes the only systematic difference to assert itself between the experimental subjects and the controls in the studies here reported. So, until some other systematic cause of the difference between the two groups is found, it seems most reasonable to acknowledge the suggestions offered by the figures obtained and by the general considerations.

Perhaps some more clear-cut results might be obtained under better experimental conditions. The statistical analysis of the figures by Director Helge Petersen includes also some curves which were not mentioned in the preceding. They were all obtained from persons with a rate of metabolism under 110 % — from determinations carried out on ambulant subjects under more quiet conditions than the aforementioned. The curves obtained from the 13 fasting subjects (students and unemployed), including the 20 curves from one person, are to be taken chiefly as preliminary studies aimed in particular to show whether the magnet would

have a stronger influence on one part of the body than on another — something which was found not to be the case. In these experiments the pole of the magnet was in direct contact with the skin.

The remaining 22 curves (Group A) were obtained from ambulant patients who prior to this examination had kept a preliminary low protein and fat diet for 2 days. Of these curves 85 % showed an increase in the metabolism under the closing of the current to the magnet in the latter part of the curve. This may perhaps be taken to indicate that better results may be obtained by having the experimental subjects keep a preliminary diet poor in protein and fat before the examination.

Finally, the curves presented in Figs. 3 and 2 suggest that better results might also be obtained with a select material of experimental subjects with a standard metabolism falling within the values which in the present experiments were found to give the greatest results. But, naturally, it will be difficult to obtain a large material of experimental subjects in whom the rate of metabolism falls within relatively narrow limits.

Recently an expert on metabolism has called my attention to the circumstance that on exposure to the influence of a factor which shifts the rate of metabolism to a new level, it will take a certain length of time before a new smooth curve may be obtained — about five min., sometimes shorter and sometimes longer. So, when I have followed the metabolism only for 5 min. after the current was connected with the magnet, my measuring could not be sure to represent a curve in final equilibrium.

The metabolism apparatus being constructed for the purpose of reading the result when there is balance in the system man-spirometer, I have employed it outside its real purpose. Presumably, however, this will not alter the result: that a disturbance involves the oxygen absorption in the latter part of the curve as compared with the first part. And this is the interesting point, not the absolute values for the oxygen absorption in the latter part of the curve.

When my curves cover merely a period of $8 + 5$ min., it is largely because I assumed that the experimental subjects might tire if the experiment was to last much longer, and then the metabolism would increase. Previously I have carried out some experiments with longer curves, but they were performed on persons

with a normal rate of metabolism, and the result appeared to be a rise in metabolism when the magnet was applied — that is, the same as happened when the subject tired. So I adopted the technique employed in the experiments presented here.

It is also to be mentioned that I have obtained some curves covering a period of about 30 min., in which the metabolism rose when the magnet was connected with the current, and decreased when the current was broken. This finding was no constant phenomenon, however, and these experiments were carried out in the course of the preliminary studies, under experimental conditions others than those for the present material, and hence they are not included in this report, although they appear directly convincing. But the quick changes observed may perhaps be taken to indicate that balance is established more rapidly under the influence of the magnet than under work. The above-mentioned objection is based on experiments carried out under constant work.

The unquiet conditions under which the metabolism was determined on the present material are not in keeping with the conditions for the employment of the apparatus. But, as mentioned, the aim of these experiments was to demonstrate the presence of differences from the application and non-application of the magnetism, not to find the absolute values for the influence of this treatment, and in this respect they appear to have been successful even though it has to be admitted that better experimental conditions probably would have yielded nicer results.

De la méningo — encéphalite post rubéolique.

Par

Dr. E. F. J. H. FALGER.

(Ce travail est parvenu à la rédaction le 29 Mars 1944).

Dans les anciens manuels la rubéole est décrite comme une maladie tout à fait inoffensive; ce n'est que dans les manuels les plus récents et dans les articles parus dans les périodiques des dernières années qu'on mentionne parfois des complications.

C'est ainsi que Glanzmann a décrit des complications avec une angine folliculeuse et une otite moyenne et que König et Potter ont constaté de violentes myalgies dorsales et lombaires et l'hydropisie de plusieurs articulations. Ces cas se rapportaient tous à des adultes.

Au printemps de l'année 1941 il y eut dans la contrée du Zaan une épidémie de rubéole, qui frappa souvent aussi des adultes, dont plusieurs étaient très malades et se plaignaient de douleurs musculaires et articulaires (communication personnelle du docteur H. Hagtingius). Pendant cette épidémie nous avons pu constater chez une femme de 26 ans, une complication se rapportant spécialement au système cérébro-spinal.

La malade avait eu en 1925 une pleurésie du côté gauche, après cela elle jouissait d'une bonne santé. Le 13 avril 1941 elle était allée voir une soeur qui avait la rubéole. Le 28 avril elle consulta son médecin le docteur Berkel qui remarqua un exanthème caractéristique de la rubéole, spécialement sur le visage, le cou et les jambes. Elle avait en outre une tuméfaction générale des glandes, une légère conjonctivite, les amygdales un peu grossies et les glandes

vomiting may be present, and the patient often suffers from a headache.

The development of the illness varies according to the severity of the particular case. With the milder forms, the cough and the dyspnea disappear within a few days, and in the more severe cases after one or two weeks. The symptoms usually persisting longest are fatigue and, in some patients, a headache. When the poisoning is more severe the signs from the lungs develop into pulmonary edema. Physical examination reveals signs of bronchitis and infiltration in the lungs, and the sputum is frothy and blood-streaked. In these cases the prognosis is grave. In Schiötz's report, 50 per cent of the patients in whom definite pulmonary edema developed expired. Of the patients described in the present paper, 4 of those with severe pulmonary edema died, while only 2 (cases 2 and 16) who yielded sputum typical of this condition survived.

Among the more uncommon symptoms mention may be made of convulsions, which occurred before death in case 14, and tremor, which was present in case 7 but could no longer be demonstrated after a couple of weeks. No other signs from the cerebral regions were observed. In the more severe cases, however, a thorough neurologic examination could not be made, owing to the poor condition of the patient.

The temperature shows, as a rule, a moderate rise in connection with the onset of the later period of symptoms. The highest temperature recorded at this stage appears to be 39.1° C but in most instances it was much lower. In the less severe cases the temperature elevation soon subsides again, while in the fatal cases it may rise prior to death. In some of the cases of medium severity in which recovery occurred there was an elevation lasting for a week or so. There may be a rise again in connection with the appearance of other symptoms (case 8). In no case were fits of shivering reported (cf. zinc poisoning).

The blood picture generally displays a slight increase in the number of white blood cells, with a moderate deviation to the left. In the patients with pulmonary edema an increase in the hemoglobin and red blood cells is a reflection of the desiccation. An extraordinary hematologic sign has been described by Ahlberg and Dahlberg (10), who found myelocytes in their case, a feature which in their opinion was due to irritation of the bone marrow.

Je fis l'autopsie 8 heures après le décès. La rigidité du cadavre était manifeste. En ouvrant le thorax je pus constater que le cartilage des côtes ne s'était pas calcifié et qu'il y avait des attachements du poumon gauche avec la paroi thoracique, soudures qui pouvaient facilement être détachées. Dans le lobe gauche inférieur il y avait des foyers pneumoniques, les autres lobes étaient normaux.

Le ventricule droit du coeur était très dilaté. Le foramen ovale était bien ouvert. Les valvules, les vaisseaux sanguins et les muscles du coeur étaient normaux.

La rate était gonflée et flasque. Le foie, la vésicule biliaire, l'estomac, l'intestin grêle et le gros intestin étaient normaux. La section du rein donna un résultat normal, les ligaments capsulaires se détachèrent aisément. Les organes génitaux internes étaient normaux.

Pendant l'autopsie du crâne je constatai des méninges très sanguines, elles n'étaient pas tendues et nulle part il n'y avait d'inflammations purulentes. La base du cerveau ne présentait pas non plus d'altérations pathologiques.

Le docteur F. H. Ter Poorten, qui pratiqua l'examen microscopique du cerveau fit le rapport suivant: «Partout mais surtout dans la substance blanche il y avait une infiltration de cellules péri-vasculaires qui étaient composée de cellules lymphoïdes, parfois aussi à mon avis de cellules de glia. Il y avait également, dans une certaine mesure une nécrose et une thrombose du paroi des vaisseaux. C'est bien là l'aspect qui correspond avec l'encéphalite, que nous constatons pendant les maladies infectieuses».

Nous avons donc affaire ici d'un cas de méningo-encéphalite survenu à la suite de la rubéole, de sorte qu'il faut bien penser à un rapport causal avec cette maladie.

Dans les ouvrages, qu'il m'était possible de consulter, j'ai rencontré en tout 36 cas de complications neurologiques de la rubéole.

Le Français Labougle a été le premier à mentionner un ensemble des symptômes de la méningite se rapportant à cette maladie. L'article parut au commencement du vingtième siècle; le malade était soldat.

tuméfiées derrière les oreilles. La malade se plaignait de légers maux de tête, mais elle se sentait si peu malade, qu'elle pouvait vaquer à ses occupations dans le ménage. Le 5 mai elle se plaignit de mal de gorge, la température s'éleva à 39.3, elle se sentait un peu étourdi et apathique. Le lendemain on trouva la malade évanouie dans son lit; c'est alors qu'on la transporta au plus vite à l'hôpital.

Status praesens:

La malade était dans un coma profond. Elle avait la respiration de Cheyne Stokes. Il y avait un strabisme convergent, les réactions des pupilles étaient légèrement positives à la lumière. Le fond de l'oeil était normal des deux côtés. Les muqueuses de la bouche et des tonsilles étaient chargées de moisissure. Les glandes lymphatiques n'étaient pas tuméfiées, celles derrière les oreilles non plus. L'exanthème avait disparu. Le cœur ni les poumons ne présentaient des anomalies. La pression vasculaire était 132/90 Riva Rocci. Le pouls était régulier et égal et la fréquence était de 100 battements par minute. Pas d'anomalies en palpant les organes du ventre; le foie et la rate n'étaient pas enflés. Il était impossible de provoquer les mouvements réflexes du tendon de genou et du tendon d'Achille, il n'y avait pas de mouvements réflexes pathologiques. Le symptôme de Kernig était positif et il y avait une légère raideur de la nuque. Dans l'urine il y avait une trace d'albumine assez bien d'urobiline, pas de sucre; dans le sédiment il y avait quelques leucocytes. La sédimentation des globules rouges était de 13 et de 34 mm après 1 heure et après 2 heures.

L'analyse morphologique du sang était comme suit: haémoglobine 88 %; 4.3 millions d'hématics et 5200 leucocytes par mm³. Basoph. 1, globules en bâtonnet 5, polynucléaires segmentés 64, lymphocytes 22, mononucléaires 8; on comptait 2 % cellules plasmiques. Le sang contenait 600 mg d'urée par litre. On constata une pression de 19 cm d'eau pendant la ponction lombaire. La liqueur lombaire était limpide. Les réactions de Nonne et Pandey étaient positives; le nombre de cellules était de 101 par cm³, c'était presque exclusivement des lymphocytes, il n'y avait pas de microbes et aussi les bouillons de culture restèrent stériles.

Un traitement avec une forte dose de sulfapyridine n'eut pas de succès. La malade mourut 24 heures après l'admission à l'hôpital.

d'endroits des accumulations périvasculaires de lymphocytes et de polynucléaires, certains vaisseaux sanguins étaient entourés d'érythrocytes. Le diagnostic anatomique détermina un cas d'encéphalite.

Un autre malade, un garconnet de 3 ans s'évanouit tout à coup 3 jours après l'exanthème. On trouva 100 cellules par mm³ (92 % de lymphocytes) dans l'humeur lombaire et une pression élevée. Le lendemain l'enfant se rétablit et six jours plus tard il quitta l'hôpital entièrement guéri.

Pendant cette épidémie qui frappa aussi beaucoup d'adultes, les complications neurologiques se limitèrent aux enfants.

Carriéu, Laury et Bouchet communiquèrent leurs résultats après une épidémie dans un village aux environs de Montpellier, où sur un total de 132 élèves, 96 élèves eurent la rubéole. Dans la majorité des cas la maladie ne dura qu'un jour. Souvent ils constatèrent chez leurs petits malades d'abondants saignements de nez et dans de nombreux cas ils virent 8 jours après l'exanthème des desquamations des mains, des genoux et des pieds; en rapport avec ceci il firent ressortir particulièrement qu'il s'agissait réellement de malades souffrant de la rubéole ayant l'exanthème et la tuméfaction des glandes caractéristiques de la rubéole; selon les auteurs il n'y avait pas d'infection de fièvre scarlatine. Pendant cette épidémie 2 enfants de 4 et 5 ans moururent le 3e jour après l'exanthème; des symptômes d'encéphalite accompagnée d'une forte fièvre et de convulsions avaient paru, qui causèrent rapidement la mort. A plusieurs reprises ils virent aussi après une diminution de la fièvre, que celle-ci augmenta de nouveau quelques jours plus tard et qu'il y avait en même temps une suppuration des glandes lymphatiques du cou; un de ces malades succomba aussi.

Le virus de cette épidémie était donc très virulent, vu que sur un nombre relativement restreint de malades il y eut 3 cas avec une issue mortelle.

Au printemps de l'année 1929 il y avait à Paris une épidémie de rubéole pendant laquelle Debré, Rurquety et Broca constatèrent que deux enfants avaient l'encéphalite. Un enfant de 7 ans tomba soudain 3 jours après l'exanthème dans un coma accompagné ci et là de contractions musculaires, d'une agitation motrice, de trismus et de spasmes musculaires toniques, qui faisaient penser au tétanos en outre il y avait des spasmes du larynx, une déviation conjuguée

vers la gauche et une fièvre montant à 41 degrés avec une fréquence du pouls de 160 battements; il n'y avait pas de raideur de la nuque pas de symptômes de Kernig. La pression de l'humeur lombaire était augmentée et on pouvait compter 23 lymphocytes par mm^3 , les bouillons de culture restèrent stériles. Deux jours plus tard l'enfant revint à lui et quelques jours après le malade était entièrement rétabli et plus tard on ne trouva pas non plus d'anomalies neurologiques. Un autre enfant de 8 ans eut également le 3^e jour un évanouissement accompagné de symptômes semblables le nombre de lymphocytes dans l'humeur lombaire montait ici à 400 lymphocytes par mm^3 . Trois semaines après cette grave maladie qui faisait craindre une issue mortelle, cet enfant-ci était également entièrement guéri et plus tard il n'avait plus aucun symptôme du côté du système cérébro-spinal.

Ces auteurs pensaient pouvoir diagnostiquer ici une «encéphalitique rubéolique» qui serait caractérisée par le début suraigu, la forte fièvre, l'agitation motrice et par des spasmes du larynx, le trismus et l'épisthotonus, une forme de maladie très grave qui prit tout à coup une tournure favorable.

Merrit et Korkoff virent aussi pendant une épidémie de rubéole à Massachussetts chez 3 enfants, 3 à 4 jours après le commencement de l'exanthème, un syndrome avec une léthargie soudaine accompagnée de contractions musculaires et d'agitation motrice, syndrome qui présente beaucoup d'analogie avec «l'encéphalite rubéolique», l'état général n'était cependant pas si grave que chez les malades de Debré c.s.

Chez tous les malades ils trouvèrent presque exclusivement des lymphocytes dans l'humeur lombaire et ici aussi un rétablissement complet suivit après un laps de temps relativement court. Les auteurs virent encore un homme de 33 ans, qui eut le 4^e jour après l'exanthème une aphasie accompagnée d'un nystagmus et du côté gauche les mouvements réflexes de Babinsky; deux jours plus tard ces symptômes disparurent de nouveau complètement et pour de bon.

Davison et Friedfeld constatèrent l'encéphalite après la rubéole dans 6 cas, dont 3 eurent une issue mortelle. Dans un de ces cas il s'agissait d'un homme de 22 ans, qui eut, 4 jours après le commencement de l'exanthème une certaine lourdeur dans la tête, accompagnée d'une légère agitation motrice: le lendemain il eut tout à

coup des convulsions, un nystagmus et une léthargie profonde avec le symptôme de Kernig et des deux côtés les mouvements réflexes de Babinsky. Le jour suivant le malade mourut après que la fièvre fut montée à 43. L'humeur lombaire était stérile et ne contenait presque exclusivement que des lymphocytes. L'analyse microscopique du cerveau montra des foyers disséminés de démyélinisation autour des vaisseaux sanguins, surtout autour des petites veines, le tout accompagné de destruction de myéline, de cylindres-axe et de tissu de glia. Les espaces périvasculaires étaient remplis de cellules de microglia, de lymphocytes, de cellules plasmatiques et de cellules d'endothélium. En outre il y avait des cellules endothéliales tuméfiées dans les vaisseaux avec des thrombi, des hémorragies périvasculaires et des changements locaux de dégénération lipoïde.

Il mourut encore une femme de 23 ans après une maladie de 7 jours et une petite fille de 8 ans dans un accès d'épilepsie quelques jours après le commencement de l'exanthème.

Les 3 autres malades parmi lesquels il y avait un jeune homme de 19 ans se rétablirent complètement de l'encéphalite.

Potter et Skinner font chacun également mention d'un autre cas de méningite cérébro-spinale après la rubéole qui eut un cours favorable, tout comme Read dont pourtant le malade, après un an se sentait encore vite fatigué, plus tard ce symptôme disparut également.

De Gennes, Célice et Gautrou nous parlent encore d'une femme de 26 ans, qui, 3 jours avant l'exanthème de la rubéole, montra des symptômes prodromiques sous forme de maux de tête violents et de vomissements. Le 5e jour après le commencement de l'exanthème il se déclara un état qui ressemblait au délire avec une forte raideur de la nuque et des symptômes de Kernig; dans l'humeur lombaire on trouva 90 lymphocytes. La méningite guérit tout à fait, de sorte que, 3 semaines plus tard, la malade était complètement rétablie.

Zadik mentionne un cas d'un garçonnet de 4 ans chez qui on diagnostiqua d'abord une méningite épidémique. Le 3e jour de la maladie lorsque les symptômes de la méningite avaient déjà disparu, il se forma un exanthème classique de rubéole accompagné de tuméfaction des glandes derrière l'oreille et d'augmentation des cellules plasmatiques dans le sang (6—8 %). Ici le virus avait

done déjà atteint le système nerveux central pendant la période d'incubation de la rubéole.

En rapport avec ce qui précède je mentionne de pareilles observations par rapport à la rougeole chez Glanzmann et Solow; à diverses reprises ces écrivains constatèrent notamment une encéphalite avant l'exanthème de la rougeole. Ces cas-ci ne furent pas suivis de guérison complète; une légère débilité, de l'aphasie et des troubles moteurs persistèrent.

Si nous passons en revue les cas observés dans la littérature et le cas mentionné par nous, nous constatons que dans 22 des 36 cas, la méningo-encéphalite se déclarèrent après la rubéole chez des adultes. Chez les enfants atteints, l'âge variait de 3 à 14 ans. Dans 8 cas (3 enfants en 5 adultes) la complication était mortelle (mortalité $\pm 22\%$).

Il paraît donc que le virus de la rubéole est relativement plus dangereux pour l'adulte que pour l'enfant.

La méningo-encéphalite rubéolique se manifestait 3 à 7 jours après le commencement de l'exanthème, excepté dans le cas Zadik, puisque ici les complications neurologiques précédèrent la maladie.

A remarquer que dans la plupart des cas les complications neurologiques prennent dès le début une forme très aiguë et disparaissent vite et totalement dans les cas, où l'issue n'est pas mortelle. Dans l'humeur lombaire on trouve presque exclusivement des lymphocytes, il n'y avait jamais des microbes. Dans les cas sans issue mortelle, il y eut toujours guérison complète; sous ce rapport l'encéphalite par suite de la rubéole se distingue avantageusement de celle qui survient après la rougeole et la vaccination contre la variole. Dans ces cas d'encéphalite la mortalité est sans doute moins grande $\pm 10\%$ (Glanzmann) mais dans 65 % des cas des malades guéris, ceux-ci restaient souffrant des suites, sous forme d'ataxie, de faiblesse musculaire, d'épilepsie, de débilité, de démence et de changements de caractère. Probablement le virus de la rubéole ne cause donc pas de changements irréparables dans le système cérébro-spinal.

Les changements anatomiques du système nerveux, les infiltrations périvasculaires des lymphocytes, les cellules plasmatiques, les cellules de l'endothélium, des tuméfactions vasculaires

de l'endothélium avec des thrombis et des hémorragies périvasculaires ci et là dans la substance grise sont les mêmes que dans l'encéphalite à la suite des maladies infectieuses.

Le début très aigu des symptômes cérébraux après la rubéole est très remarquable et ce symptôme plaiderait pour la supposition (qui a déjà été émise plusieurs fois pour l'encéphalite survenue à la suite de la rougeole et de la vaccination contre la variole) qu'on doit attribuer les anomalies dans le cerveau à des changements causés par l'anaphylaxie à la suite des toxines de la rubéole.

Les changements vasculaires et la localisation périvasculaire des lésions portent à croire que les toxiques nuisibles dans les vaisseaux sanguins se répandent (tout à coup) dans les tissus environnants (favorisé par une perméabilité anormale) et la poussée du sang dans les veines auxquels s'ajoute probablement la plus grande perméabilité de la barrière sang-liquor qui joue un rôle important dans la sensibilisation du système cérébro-spinal.

Résumé.

Description d'un cas de méningo-encéphalite rubéolique avec issue mortelle chez une femme de 26 ans. Nous avons signalé le début très aigu en général des complications neurologiques après la rubéole, la présence presque exclusive des lymphocytes dans la liqueur lombaire qui est toujours stérile et la probabilité que les changements anatomiques du système cérébrospinal sont causés par une réaction anaphylactique sur les toxiques de la rubéole.

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Eosinophil granuloma of Bone — Schüller-Christian's disease.

By

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In 1929 Finzi described a peculiar morbid condition which he called »eosinophil myeloma». It was the case of a boy, 15 years old, on whose forehead a bump appeared without any known cause — in particular with a negative history as to preceding traumatic injury. Roentgenography showed a sharply defined clearing, 20×8 mm, due to a tumor-like tissue consisting of a cellular, richly vascularized, reticular stroma, the meshes of which contained numerous eosinophil cells together with neutrophil leucocytes and a few giant-cells. The blood showed eosinophilia.

Since then, several similar cases have been reported. Schairer (2 cases) considers the condition a peculiar form of osteomyelitis, and emphasizes that the granuloma is built up of reticular cells with many eosinophil leucocytes and giant-cells, besides the presence of iron pigment. Otani & Ehrlich, who have reported 7 cases, designate the condition as »solitary granuloma of bone». Possibly a case reported by Mignon belongs to this group too, but no histological findings were given.

In 1940 Lichtenstein & Jaffe reported 4 cases, and Mallory 4 additional cases. These authors advocated the view that the condition involves a disease *sui generis* of unknown etiology (they

think that a virus may possibly be the cause), the more essential characteristics of which are as follows:

In a child or young person a painful tumor of a bone, most often a membranous bone, makes its appearance. Roentgenography reveals a solitary, sharply defined, defect in the bone, sometimes with swelling of the corresponding soft parts.

The *histological* findings are as described above: a granuloma made up of reticular cells with numerous eosinophil leucocytes, sometimes also giant-cells of the osteoclast type. The blood and sternal bone marrow may show a moderate eosinophilia (Finzi, Lichtenstein & Jaffe, Schairer).

The differential diagnosis involves particularly osteomyelitis Ewing's sarcoma, cyst of bone and Schüller-Christian's disease. The prognosis is good, as the granulomas heal with or without treatment (X-ray treatment, curettage).

The etiology is unknown. Bacteriological studies have turned out negative (Otani-Ehrlich, Schairer). In several cases, however, the development of the eosinophil granuloma has been preceded by traumatic injury, often severe (Mallory's cases, Mignon's case, 5 of Otani & Ehrlich's 7 cases (one of them with 2 traumas and 2 corresponding foci), and 1 of Schairer's cases).

So there does occur a morphologically and symptomatologically rather well-characterized nosographic picture, «eosinophil granuloma of bone», but it is doubtful whether it be justified to consider this condition a disease *sui generis*. Indeed, this has been questioned by various authors. Furthermore, the cases we have observed suggest a different classification of this syndrome.

Case 1.

Girl, 9 years old. (Neurosurg. Dep. of the Rigshospital, Rec. No. 4730.)

The patient gave a past history of good health. 3 months before her admission a bump on her forehead was noticed accidentally. Her parents took it to be an inflammation and treated her with hot compresses. Her condition was aggravated, however, and she was hospitalized.

Physical examination showed a 2 cm. — wide depression in the frontal bone, to the right of the midline, 1 cm. below the hair border. No tenderness on palpation. No pulsation.

Roentgenography: In the frontal bone, to the right of the midline an irregular defect is seen, measuring about 4 cm in diameter, extending through the entire thickness of the bone. A lateral view shows a slight bulging of the thin lamina externa in the periphery of the defect.

X-ray diagnosis: *Frontal ostitis*.

Other examinations showed normal conditions. Ventriculography: No abnormality. Hemoglobin: 85 %. Sedimentation rate: 8 mm/1 hr. Serum calcium: 10.3 mg %. Serum pH phosphorus: 3.9 mg %. Urine: No abnormal elements.

On operation the bony defect was found to be filled with a greyish fibrinous granulation tissue, extending out on the outer and, especially, inner surface of the skull, where it was adherent to the dura but could be detached without difficulty. Reexamination on 16/1/44, 2 months after the operation: X-ray examination of the entire bone system revealed no other foci.

Microscopic examination. A specimen, tissue from the frontal bone, shows a granulation tissue which in most places is very cellular and richly vascularized, with numerous eosinophil leucocytes, histiocytes and hemosiderin-containing macrophages with transition to large irregular multinuclear cells. There is a considerable accumulation of blood pigment. No xanthoma cells are seen.

Epicrisis: In a girl, 9 years old, a solitary bump appears on the forehead without any known cause. There is found to be a pronounced bone defect, and histologically the bump is built like an eosinophil granuloma of bone. The »bump» was removed operatively.

Six months after the commencement of her illness the girl was free from symptoms; in particular roentgenography of the skeleton revealed no other foci.

Observation period: 6 months.

Case 2.

Girl, 8 years old. (Radium Station, Rec. No. 30, 852.)

About 18 months prior to the onset of the present lesion the patient suffered a rather severe traumatic injury to the pudental region when she fell against the edge of a board. Two months before her present illness she suffered a concussion of the brain, followed by an attack of pneumonia. Shortly after this, she commenced to drag her left leg, and she complained of tenderness of the trochanteric region. Her appetite was poor, her temperature subfebrile (38°—38.5°).

Roentgenography: In the upper two-thirds of the inferior branch of the left pubic bone, near the symphysis, the structure of the bone is completely effaced by a destructive process measuring 12 × 35 mm. Also the medial contour is effaced: There is no tumor of the soft parts, no new formation of bone.

X-ray diagnosis: Destructive process in the left pubic bone. No changes in the rest of the skeleton.

Biopsy (drilling ad modum Christiansen) revealed a typical eosinophil granuloma (see below).

Under X-ray treatment (450 r anteriorly and 500 r inferiorly) the process disappeared completely within 6 months. But now an area of tender-

ness appeared in the right arm, and roentgenography showed here a *new focus*, a sharply defined area of rarefaction, $\frac{1}{2} \times 3$ cm, in the upper part of the shaft of the humerus.

Of other examinations the following are to be mentioned: Hemoglobin: 89 %. Red blood count: 4.25 millions. White blood count: 9240. Sedimentation rate: 25 mm/1 hr. Serum calcium: 10.8 and 11.2 mg %. Serum phosphorus: 4.78 and 4.60 mg % Phosphatase: 23. Blood cholesterol: 173 and 169 mg %. Urine: No abnormal elements.

Microscopic examination: The specimen, from the process in the pubic bone, shows large, compact flakes of a very cellular tissue, built up of uniform, rather large, round or elongated cells, with varying amounts of cytoplasm and round nuclei. The cells vary considerably in size; many mitoses are seen. V. Gieson stain shows no stroma proper, but scattered fine streaks of collagenic connective tissue, with scanty delicate blood vessels, in the intervals between the cells. This picture of a homogeneous tissue rich in cells, sending peripheral cords in between the surrounding connective and muscular tissue, may remind somewhat of tumor tissue (Fig. 1). Scattered about in this tissue, however, large clusters of polynuclear eosinophil leucocytes are seen (Fig. 2), which also fill some of the scanty small vessels. No typical granulation tissue is seen; and no giant-cells, nor foamy cells are seen. In some areas the cells described above, which have to be regarded as reticulo-histiocytes, present a cytoplasm with a considerable number of tiny vacuoles. No accumulation of blood pigment is seen.

Epicrisis: In a girl, 8 years old, an eosinophil granuloma develops in the pubic bone 1 $\frac{1}{2}$ years after a traumatic injury. No changes are found in the rest of the skeleton at that time. After X-ray treatment this process disappears within 6 months, but is followed by a new focus in the right humerus. Microscopic examination shows eosinophil granuloma.

Observation period: 8 months.

Case 3.

Boy, 3 years old. (Neurosurgical Dep. of Aarhus City Hospital, Rec. No. 284.) *

The patient is No. 6 of 6 children; all the others are well. Through the past year he has had a gradually increasing «tumor» in the left orbit, with diminution of the palpebral fissure. The tumor is said to vary in size, swelling when the patient catches a cold. The tumor arises from the roof of the orbit, and the eyeball is displaced a little downwards and medially. The tumor is smooth, elongated, not tender.

Roentgenography shows irregular destruction of the upper margin of the left orbit, above which a couple of irregular areas of rarefaction of the

* We are obliged to Dr. Rich. Malmros, Chief Physician, for permission to publish this case.

bone are seen, about 1 cm in diameter. On operation a tumor is removed, measuring about $1\frac{1}{2} \times 2 \times 3$ cm and extending along the entire upper margin of the orbit. The tissue of the tumor is soft, greyish and yellowish in color.

X-ray examination of the rest of the skeleton shows no abnormality in the extremities, but the *wing of the right ileum* presents an area of bone destruction, $3\frac{1}{2} \times 4$ cm, consisting in several small, rather sharply defined rarefactions, partially confluent. No abnormality is seen in the scapulae and ribs. Of other examinations, the following may be mentioned: Hemoglobin: 85 %. Red blood count: 5.24 millions. White blood count: 10000. Blood sugar: 112 mg %. Urine: Diuresis normal. No abnormal elements. No disturbances of vision.

Microscopic examination: Tissue from the roof of the orbit shows somewhat varying features in the various fragments. In some places there is a diffuse reticulo-histiocytic proliferation with a rather homogeneous tissue, rich in cells, as in Case 2, though somewhat more richly vascularized. In other places the tissue is looser, presenting the character of granulation tissue with numerous new-formed blood vessels, leucocytes, especially eosinophils, and numerous histiocytes, which in several areas appear as macrophages with transition to giant-cells with marginal nuclei (Touton cells), up to 30—40 of which are seen in one area (Fig. 3). Eosinophils are encountered here too, sometimes in clusters. In some places the histiocytes are very large, showing phagocytosis, whereas no fully developed xanthoma cells occur. No blood pigment is seen.

Epicrisis. A boy, 3 years old, has a soft tumor of the roof of the left orbit, where roentgenography reveals a defect in the bone. Another defect is found in the wing of the right ileum. Microscopic examination shows the picture described as characteristic of eosinophil granuloma and, in addition, beginning lipoid phagocytosis and the presence of Touton cells.

Observation period 15 months.

Case 4.

Boy, 5 years old. (Radium Station, Rec. No. 26, 778.)

The boy is a twin; the other twin is well.

At the age of 3 years the patient had an attack of acute otitis media. Shortly after, a «bump» was noticed on the right side of his head. He had no complaints. He was admitted to the Neurosurgical Dep. of the Rigs-hospital, where roentgenography revealed a defect in the skull. Ventriculography and test puncture were performed. On operation the bump was removed together with the surrounding bone and a piece of the dura to which the brownish-yellow granulation tissue-like tumor tissue was adherent. After this he was transferred to the Radium Station.

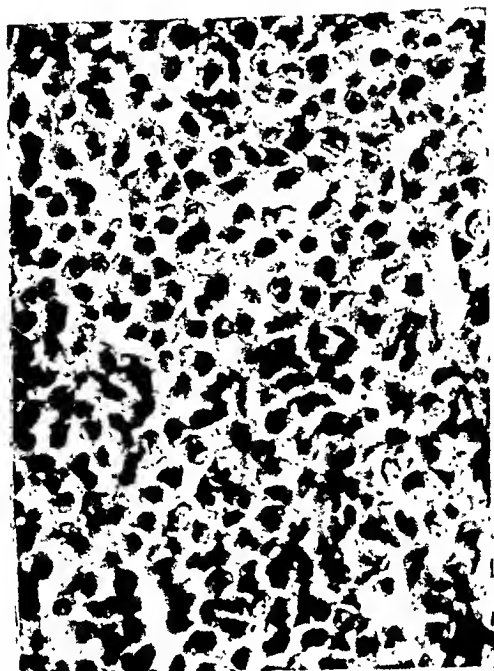


Fig. 1. Case 2. Tissue of reticulum cells, uniformly rich in cells. (Hyperplastic-proliferative phase). Hematoxylin-eosin. Magnif. $\times 470$.

At this time the boy could not yet talk, although he then was over 3 years old.

Physical examination revealed no abnormality apart from the trepanation defect in the skull.

Röntgenography of the entire skeleton revealed in the *right mandible* a large irregular area of rarefaction below the anlage for the posterior molar, extending to the surface of the bone and leaving the compact bone merely as a thin sheet, 1 mm in thickness. The lateral half of the *left clavicle* presented an area of rarefaction, measuring $1 \times 1\frac{1}{2}$ cm and surrounded by irregularly wide-meshed osseous tissue. Also the *right clavicle* showed an area of rarefaction, 4×6 mm. No abnormalities were seen in the thorax, vertebral column, pelvis and extremities.

Other examinations: Hemoglobin: 76 %. Red blood count: 3.65 million. White blood count: 5200. Differential count normal; in particular, no eosinophilia. Sedimentation rate: 23 mm/1 hr. Serum calcium: 10.8 mg %. Serum phosphorus: 4.16 mg %. Blood cholesterol: 164—165 mg %. Formol gel: Negative. Gonadotropin in urine: 0. Urine: No abnormal elements.

The patient was given X-ray treatment, and he was improving when he was discharged. He was readmitted, however, when — 3 weeks after a fall, in which he suffered a hematoma in the occipital region — a soft tumor developed at this site, accompanied by discharge from the right

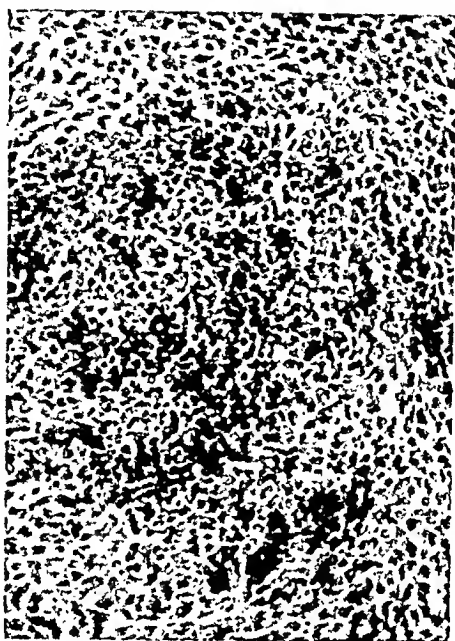


Fig. 2. Case 2. Clusters of eosinophil leucocytes surrounded by reticulum cells. Hematoxylin-eosin. Magnif. $\times 240$.

ear. In the right side of the occipital region a round soft swelling was palpable, and X-ray examination showed here a sharply defined defect in the bone, 3 cm in diameter.

The patient was given X-ray treatment, to which the lesion yielded with a decrease in the bony defect and disappearance of the swelling.

X-ray examination of the rest of the skeleton showed no abnormality. 4 months later there were no symptoms of the lesion, no sign of any recurrence.

Microscopic examination: Tissue from the dura shows a diffusely extending granulation tissue with numerous fine capillaries and masses of polymorphonuclear leucocytes, including numerous eosinophils in large clusters (Fig. 4), lymphocytes, histiocytes and macrophages. Extensive hemorrhage is seen, also accumulations of blood pigments, which partly is undergoing phagocytosis. Numerous larger macrophages and giant-cells are seen, especially in areas where the tissue is looser and meshy in structure; in some places these cells resemble osteoclasts with up to a dozen nuclei of irregular location (Fig. 5), whereas other areas appear to show transitions to typical Touton cells with peripheral nuclei.

On the surface of the dura, separated from the granulation tissue, an entirely xanthomatous patch is seen, with large typical foamy cells (Fig. 6) and a few Touton cells.

On Foot staining an extraordinarily dense and fine network of argentaftine fibrils is seen.

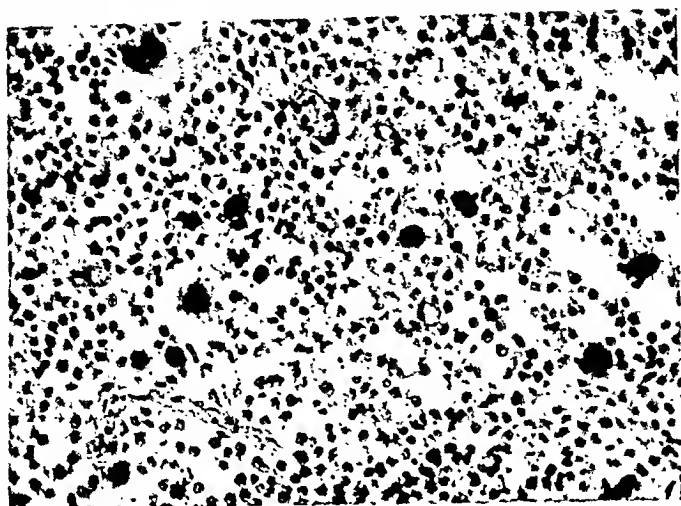


Fig. 3. Case 3. Granulation tissue with numerous giant-cells of Touton type as sign of beginning lipoid phagocytosis. Hematoxylin-cosin. Magnif. $\times 240$.

Epicrisis: In a boy, 3 years old, a bump appeared on the right side of the head without any known cause. A bone defect was demonstrated here. Three additional foci of similar character were found in the mandible and clavicles, and later, another focus appeared in the occipital region after a traumatic injury.

Microscopy shows a picture of eosinophil granuloma of bone and also an area of xanthoma tissue with large foamy cells and Touton cells.

The patient has been free from symptoms for the last 6 months. Observation period: 3 years.

Case 5.

Boy, 5 years old. (Radium Station, Rec. No. 1313.)

The patient is a twin, No. 7 of 8 children.

Rickets at the age of 1 year; otherwise well till the onset of the present lesion. This commenced at the age of 2 years, when a red bump was noticed accidentally on the right cheek. The bump was tender to pressure and increased gradually in size, reaching a diameter of 3—4 cm. Then he was admitted to hospital where an incision was made into the sarcoma-like tumor, and tissue removed herefrom was taken to be Ewing's sarcoma with inflammatory changes, on which account the patient was transferred to the Radium Station. Here he was found to be a little anemic and rather thin, with subfebrile temperature. The aforementioned tumor, measuring 5 \times 5 cm, was found in the zygomatic region; the incision on top was filled with tissue looking like granulation tissue. In the retromandibular region

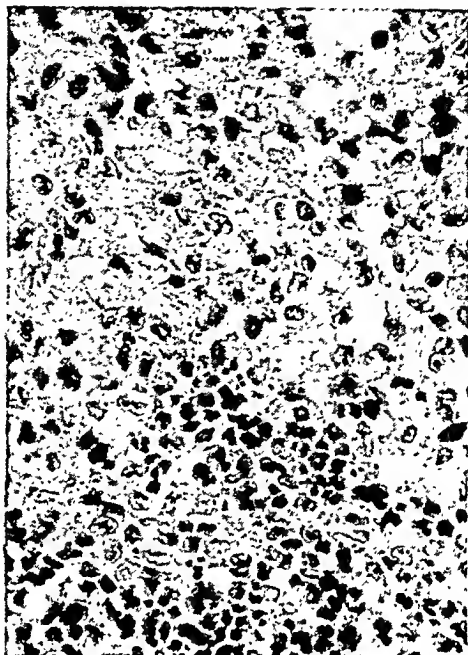


Fig. 4. Case 4. Eosinophil cells in clusters and reticulum cells. Hematoxylin-eosin. Magnif. $\times 470$.

6—7 slightly enlarged lymph nodes could be made out. In addition the boy presented scabies.

Roentgenography revealed an area of rarefaction, sharply defined, $3\frac{1}{2}$ cm in diameter, in the right temporal region, involving the anterior part of the temporal squama and the adjacent parts of the parietal and frontal bones. No abnormality was seen in the rest of the skeleton, but the lungs presented numerous, partly confluent, blurred spots (3—4 mm in diameter), of uncertain nature. These spots remained unchanged on repeated examinations through several months.

Blood examination showed the presence of anemia (Hb. 69 %) and leucocytosis (white blood count 14700) with 46% atypical monocytoid cells; no eosinophilia. Punctate of bone marrow from the tibia showed 30 % of the same atypical cells.

Several diagnoses were considered (malignant tumor with metastases to the lungs, atypical lymphosarcomatosis or reticulosarcomatosis with metastases to the lungs and changes in the blood, atypical leukemia), and X-ray treatment was instituted with the result that the tumor in the temporal region disappeared completely in response to a total of 2000 r (while the changes in the lungs persisted). The changes in the blood subsided in a couple of months, whereafter blood examination gave normal findings (Hb; 82 %, white blood count 9600, differential count normal).

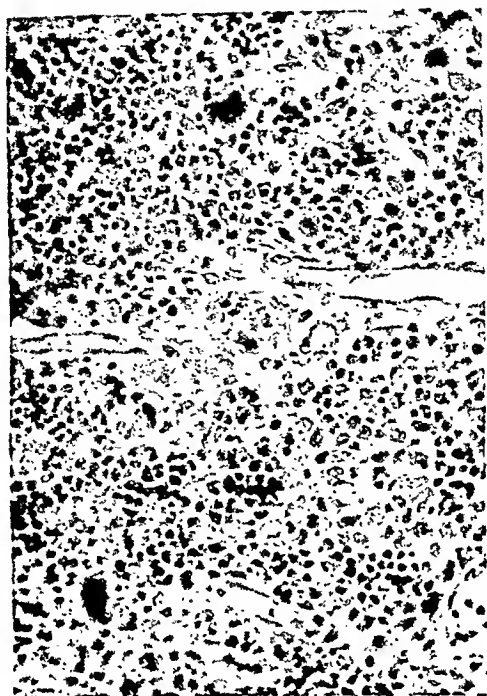


Fig. 5. Case 4. Granulation tissue with new-formed capillaries and osteoclast-like giant cells. Pronounced eosinophilia. (Granuloma phase). Hematoxylin-eosin. Magnif. $\times 210$.

Of other examinations the following may be mentioned: Blood cholesterol 160—170 mg %. Serum calcium 11.2 mg %. Serum phosphorus 6.1 mg %.

The patient got well and was discharged. One month later, however, he was readmitted with a focus in the mandible on the first molar. *Histological examination* of tissue removed herefrom (see below) showed quite the same features as had been observed in the temporal «tumor».

During the following year the classical picture of Schüller-Christian's disease developed.

Gradually numerous foci developed in various bones (the skull, mandible, scapulae, pelvis, femur and ribs) together with a skin focus in the nose.

Biopsy (scapula) still showed the same histological features (see below).

In addition, a marked degree of diabetes insipidus developed, with a diuresis exceeding 2 liters. Besides, the patient was strikingly small for his age and growth appeared to have stopped.

Blood examination now showed practically normal findings without reticulosis and without eosinophilia. Puncture of bone marrow showed normal conditions.

His condition was getting worse, but under X-ray treatment the various foci healed in the next couple of years, and his diabetes insipidus respond-

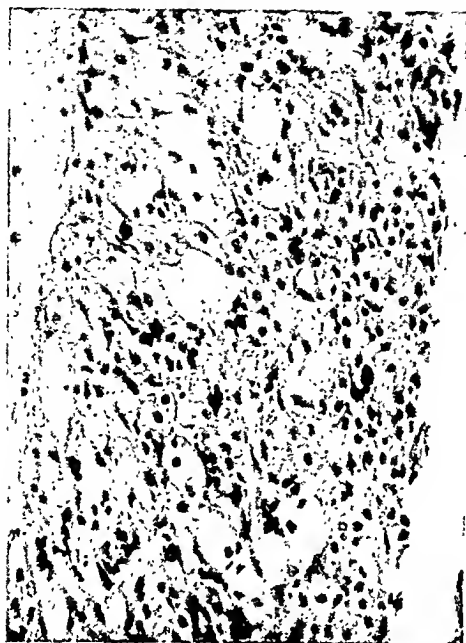


Fig. 6. Case 4. Xanthomatous tissue from the dura with typical foamy cells. (Xanthoma phase). Hematoxylin-eosin. Magnif. $\times 305$.

ed favorably to treatment with posterior pituitary lobe powderized for sniffing.

Five years after the onset of the lesion his condition was stationary, with healed foci in the bones, but with persistent diabetes insipidus and dwarfism of pituitary type.

Numerous blood examinations in the last couple of years have mostly shown normal findings. Eosinophilia was demonstrated twice, however, with 10.5 % eosinophils in a white blood count of 10960, and 8 % of 9800. Besides, a couple of bone marrow punctates have again shown the aforementioned somewhat atypical monocytoid reticulum cells.

Blood cholesterol, calcium and phosphorus have kept unchanged throughout the course of the lesion.

Microscopic examination: As in Case 2, specimens of tissue from the temporal tumor, the mandible and scapula show a slightly vascularized dense cellular tissue built up of close-packed reticulum cells. Numerous eosinophils are seen, partly enlarged clusters (Fig. 7—8), partly more scattered in the tissue. The changes are chiefly proliferating. The scanty blood vessels are filled with leucocytes, especially eosinophils. The tissue contains no giant-cells, blood pigment or xanthoma cells.

Sudan III stain: No lipoid accumulation.

Reticulin staining shows delicate, partly reticular, fibrils round the individual cells.

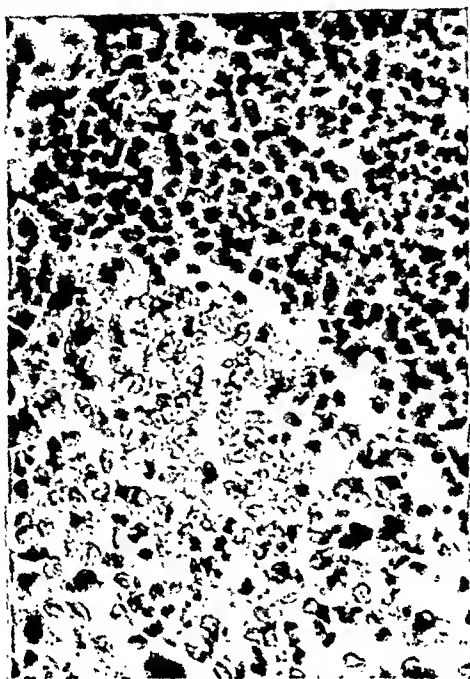


Fig. 7. Case 5. Reticulum cells and eosinophil leucocytes. Hematoxylin-eosin. Magnif. $\times 470$.

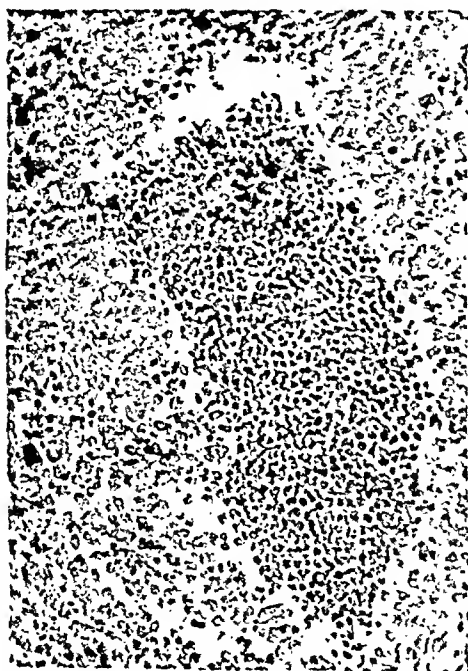


Fig. 8. Case 5. Eosinophil cells surrounded by a tissue uniformly rich in cells. Hematoxylin-eosin. Magnif. $\times 240$.

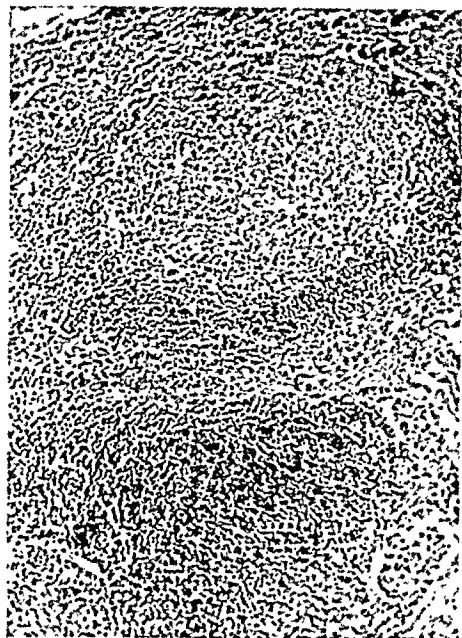


Fig. 9. Case 5. Lymph node with proliferative reticulosis and eosinophilia. Hematoxylin-eosin. Magnif. $\times 120$.

Sections from a lymph node (Fig. 9) shows pronounced reticulosis; in some places the structure is a little blurred. The sinuses contain reticulum cells and scattered eosinophils. In other areas large, light-staining, germinal centers are seen with the normal structure preserved.

Epicrisis: In a boy, 2 years old, a large »bump» appeared in the right temple, with a corresponding defect in the skull. Under X-ray treatment the process healed, but in the following year several foci developed, and finally the process was generalized, with innumerable bone foci. At this time diabetes insipidus developed too, and now the patient presented clinically a typical instance of Schüller-Christian's disease.

Microscopic examination of tissue from 3 foci showed in every instance a typical picture of eosinophil granuloma.

In addition, the bone marrow and blood showed a considerable degree of reticulosis in the early stage of the disease.

The osseous changes healed (after X-ray treatment), but diabetes insipidus and pituitary dwarfism persist.

Observation period 4 $\frac{1}{2}$ years.

Summarizing the changes presented by the patients in the 5 cases reported above, they may all be said to show a typical picture of eosinophil granuloma of bone. In all five cases the histological features are quite characteristic, but in addition, our patients present some other features which obviously place this «eosinophil granuloma of bone» as a link in Schüller-Christian's disease (see Table 1.)

As to the *clinical symptomatology*, then, these cases show all transitions from the entirely *solitary* «eosinophil granuloma» to a *universal* spreading of the affection with innumerable bone foci, continually of the same histological structure (Case 5), in a typical case of Schüller-Christian's disease with cranial defects and diabetes insipidus.

Also the clinical picture of eosinophil granuloma with «protruding foci», «soft areas in the skull», etc. in the sites of choice in the skull and pelvis is quite in keeping with the recognized initial symptoms in classical cases of Schüller-Christian's disease. Judging from our cases, the entirely solitary eosinophil granuloma appears to be of rare occurrence; often it is possible through observation for some length of time and roentgenography of the entire skeleton to demonstrate two or more foci.

Morphologically our material presents a picture corresponding

Table 1.

Writers' Cases of «Eosinophil Granuloma of Bone» Illustrating the Transition to Typical Schüller-Christian's Disease.

	Sex	Age in years	Duration of illness at last exam.	No. of foci	Remarks
Case 1	F.	9	6 months	1 (skull)	
Case 2	F.	8	8 months	2 (pubic bone, humerus)	
Case 3	M.	3	15 months	2 (skull, ileum)	
Case 4	M.	5	3 years	5 (skull (2), mandible, clavicle (2))	
Case 5	M.	2	4 1/2 years	Innumerable	Diabetes insipidus, dwarfism, changes in lungs and skin

to the one described as typical of eosinophil granuloma. But, in addition, the various cases show different developmental stages typical of the granuloma in Schüller-Christian's disease — as will be mentioned in detail below. Here it will be appropriate in particular to emphasize the occurrence of Touton cells (as evidence of lipid accumulation) and typical xanthoma tissue with foamy structure together with a characteristic granulation tissue seen respectively in Cases 3 and 4, even though these patients may only present a solitary osseous focus without other typical symptoms.

The connection between eosinophil granuloma of bone and Schüller-Christian's disease has been ventilated before (Ahlström & Welin, 1943; Green & Farber, 1943), although such illustrating intermediate lengths as the cases here presented were not known hitherto. Most American authors have refuted the possibility of such a connection between the two morbid conditions. On the other hand, several investigators, especially German, have objected to the prevailing view advanced by Rowland (1928) of Schüller-Christian's disease being primarily a disorder of the lipid metabolism analogous with Gaucher's disease and Niemann-Pick's disease, pointing out that the lesion primarily involves a granulating process, while the lipid accumulation is a secondary phenomenon.

As to Schüller-Christian's disease, we beg to refer the reader to a paper by Teilum (1942) on the clinical and autopsy findings in a case of cholesterol granulomatosis (in an adult) with a review of the pathology and histogenesis of the disease. That the lesion primarily involves a *lipoid-free* granuloma was first claimed by Ceelen and by Letterer (1933), later by Heine and Gerstel, and since by practically all pathologists who have had occasion to examine such cases.

The cases reported by Gerstel and Wätjen are particularly illustrating. After thorough study of a case previously reported by Ceelen, in particular through careful examination of the entire skeleton of a patient with classical Schüller-Christian's disease (a girl, 2 ½ years old), Gerstel found that the small, fresh foci in the skeleton are granulomas without foamy cells, whereas only »Herde in vollem Umbau» are filled with foamy cells, and that older foci show evidence of healing with fibrosis. The bone changes are described by Gerstel as »zerstörend vordringende Granulome mit

erst später erfolgreicher Lipoidablagerung». He demonstrated similar changes in the entire reticulo-endothelial system, in the liver, spleen and lymph nodes.

In Wätjen's case — a boy, 10 months old — a large granuloma was found in the jaw, and another in a rib. These granulomas were typical xanthomatous granulomas with foamy cells, but also with granulation tissue with many eosinophils; and fat cells were found too. Diffuse changes of a similar character were demonstrated in the bone marrow, though without any particular destruction of bone. Finally, the skin was the site of innumerable confluent ulcers (which had dominated the clinical picture), which histologically showed granuloma-like accumulations of large reticulum cells, but no foamy cells.

Tissue eosinophilia plays a great role in a number of previously reported cases of Schüller-Christian's disease — e.g., Henschen's Case II, in which the first histological examination showed granulation tissue with numerous polymorphonuclear eosinophil leucocytes, and Heine's case, in which the examination of 2 osseous foci, in the femur and in the frontal bone, that hardly contained any foamy cells but myriads of eosinophils, led primarily to the diagnosis, atypical lymphogranulomatosis. These and other autopsied cases show various transitions between lipoid-free granulomas and typical xanthomatous tissue. Wätjen found fat-free and fat-containing granulomas side by side, and Gerstel suggests that in the early stages of Schüller-Christian's disease we meet with primary lipoid-free granulomatous processes which subsequently may take up lipoid and thus form the fully developed foamy-cell granuloma.

It really seems strange that the American investigators who have elucidated the clinical aspects of the eosinophil granuloma of bone and studied its histology thoroughly insist so strongly upon differentiating it from Schüller-Christian's disease, while the German authors, who have emphasized the primary granulomatous nature of Schüller-Christian's disease — a view to which no American appears to subscribe — seem not to be acquainted with the clinical picture of the solitary eosinophil granuloma of bone. Ahlström & Welin (1943), in Sweden, are the first to ventilate the possibility, that the two clinical entities may have something to do with each other, although they do not wish yet to commit themselves on the

question whether or not the eosinophil granuloma of bone is a disease *sui generis*. In a work cited by Ahlström & Welin, but inaccessible to us, by Green & Farber, entitled »Eosinophilic or Solitary Granuloma of Bone» (J. Bone & Joint Surg., July 1942), comprising 10 cases of the lesion in children under 12 years, these authors advocate the view that the so-called eosinophil granuloma is a particular form of Schüller-Christian's disease.

In Ahlström & Welin's own case the patient was a boy, 1 ½ years old, with multiple foci of skeletal destruction and roentgenological signs of infiltrations round the right kidney. The changes developed successively during 3 years, but they all healed under X-ray treatment. Histological examination showed a tumor-like eosinophil granuloma without foamy cells.

Our 5 cases show, however, that there exists a quite gradual transition from the »solitary eosinophil granuloma of bone» to the fully developed Schüller-Christian syndrome. Case 5 is particularly illustrating, as here a clinically and roentgenologically established instance of Schüller-Christian's disease — with multiple foci of bone destruction, diabetes insipidus, inhibition of growth and presumably visceral manifestations — on microscopic examination of three osseous foci (in the skull, mandible, and scapula) showed each time the morbid picture without foamy cells characteristic of eosinophil granuloma.

So there seems to exist a number of forms of manifestation of this disease, from a solitary granuloma to the generalized form — forms which individually may make their appearance with or without lipid accumulations in the form of foamy cells. The different forms of manifestation are given schematically in Table 2, together with an autopsied case (Henschen's Case II).

After this, the concept »eosinophil granuloma» may hardly be maintained as a nosological entity but has to be taken as a not altogether infrequent, clinically monosymptomatic, form of Schüller-Christian's disease, which most often heals without becoming generalized, while in rare cases it is generalized and then often accompanied by other classical symptoms from the triad characteristic of Schüller-Christian's disease: multiple cranial defects, exophthalmus, and diabetes insipidus.

Schüller-Christian's disease, then, is a lesion of far greater frequency and better prognosis than generally assumed, the osseous

Table 2.

*Schematic Survey of Manifestations of Eosinophil Granuloma of Bone
Schüller-Christian's Disease.*

1. Solitary eosinophil granuloma without lipoid.	Case 1
2. Multiple " " " "	Case 2
3. " " " with Touton cells and signs of beginning lipoid phagocytosis.	Case 3
4. " " " with xanthoma tissue.	Case 4
5. Generalized development of eosinophil granuloma without lipoid, together with diabetes insipidus, dwarfism and changes in lungs and skin.	Case 5
<hr/>	
6. Generalized form (Schüller-Christian's disease)	With eosinophil lipoid-free granuloma in skull, but extensive visceral xanthomatosis, exophthalmus.
	Hensehen's Case II

foci as a rule healing rather rapidly under X-ray treatment. After this, local surgical measures must be looked upon as directly contraindicated. It will be of decisive importance, therefore, to make a sure diagnosis, and as a rule this should be based not only on the entirely clinical findings but also on the histological examination of material from a focus obtained by biopsy.

From the literature it is plainly evident that previously the biopsy findings have been misleading in many cases of Schüller-Christian's disease. This was chiefly due to the erroneous but widely accepted view that this lesion always is associated with xanthomatous transformation of the tissue. In this way, histological pictures like the ones described in our cases have been misinterpreted as tumor (myeloma, Ewing's sarcoma), lymphogranulomatosis, etc.

Here we have to keep in mind that in the present cases the morphological examination has been limited to osseous foci. From Hensehen's and other authors' accounts of the findings in cases examined post mortem it is evident that practically lipoid-free granulomas of bone may very well be associated with extensive xanthomatous changes — for instance, in the perirenal adipose tissue.

Bénard décrit une épidémie dans l'Hôpital Militaire de Versailles en 1921, pendant laquelle 291 soldats eurent la rubéole et 168 soldats la rougeole. Parmi les malades souffrant de la rubéole, il constata 13 cas où le système cérébro-spinal était atteint.

Le 6^e et le 7^e jour après l'exanthème on constata chez 4 hommes tout à coup une forte fièvre, du mal de tête et le symptôme de Kernig. Dans l'humeur lombaire on trouva 15 à 25 lymphocytes par mm³. Le lendemain de ces symptômes les malades se sentaient bien et se rétablirent complètement.

Dans 3 cas les symptômes de la méningite durèrent 3 jours, puis les malades guérirent.

Un des soldats eut soudain le 6^e jour, une méningite qui disparut le lendemain et qui revint le 3^e jour (forme remittente); elle fut suivie également ici d'une guérison complète.

L'auteur constata également un cas de «méningite à poussées multiples» pendant laquelle dans un délai de 30 jours il y eut 6 attaques caractéristiques de méningite alternant avec des périodes pendant lesquelles il n'y avait aucune plainte.

Un des malades eut une méningomyélite accompagnée d'une paralysie ascendante du type Landry, le 4^e jour après l'exanthème; 3 jours après il succomba.

Chez tous les malades on avait trouvé surtout des lymphocytes dans l'humeur lombaire, jamais on n'y trouva des microbes, les bouillons de culture restèrent toujours stériles. Pendant cette épidémie, qui ne fit que des victimes parmi les adultes, on est frappé par le grand nombre ($4\frac{1}{2}\%$) de complications neurologiques. On ne fit pas mention de complications chez les soldats souffrant de rougeole.

Briggs décrit une grande épidémie de rubéole, qui eut lieu à St. Paul Minn., pendant l'hiver de 1935 et qui frappa tout aussi souvent des adultes que des enfants. Il constata chez un garçon de 10 ans, 2 jours après l'exanthème, tout à coup une aphasie motrice accompagnée d'un nystagmus latéral, d'une paralysie partielle du bras droit et de mouvements réflexes pathologiques de la jambe droite.

Dans l'humeur lombaire on trouva 51 cellules par mm³ (98 % de lymphocytes). L'enfant mourut le lendemain. Pendant l'autopsie on trouva des pétéchies dans la substance blanche, surtout à la base du cerveau. Dans le microscope on vit en beaucoup

fibrils. In presenting these features — as emphasized especially by Letterer — lipoid granulomatosis differs from genuine reticulosis and has to be looked upon as an inflammatory, granulating process, strictly connected with the vascular and connective tissue system. This is evident from pathologic-anatomical studies on autopsied cases with spreading of the lesion to various organ systems where such processes are seen to progress along the blood vessels with granuloma formation in the adventitia — e.g., in the bone system (Gerstel) and the central nervous system (Teilum).

Besides new-formed capillaries and collagen fibrils, the granuloma phase presents numerous polymorphonuclear leucocytes, most of which are eosinophils, and also plasma cells. Further, reticular cells and histiocytes assume the character of macrophages with markedly vacuolized protoplasm and beginning lipoid phagocytosis; besides, considerable amounts of hemosiderin are often present, partly free, partly taken up by phagocytes. At the same time the tissue becomes more loose in structure, spongy. Often transitional forms are seen between macrophages and polynuclear small and large giant-cells, both typical Touton cells with marginal nuclei (Fig. 3), and cells resembling osteoclasts (Fig. 5), of which at any rate the former have to be taken as evidence of lipoid phagocytosis even though no typical xanthoma cells have made their appearance yet. Only the last-mentioned cells give the typical picture of the 3) *xanthoma phase* (Case 4, see Fig. 6), which again may go on to a 4) *fibrous stage* when the process is healing.

Summary.

1. Report is given of 5 cases of the so-called «eosinophil granuloma of bone», in children aged 2—9 years, presenting clinic-symptomalogically as well as morphologically a gradual transition to the fully developed Schüller-Christian's syndrome.

2. *Clinically* transitions were formed from the solitary «eosinophil granuloma» through cases with several osseous foci to a generalized case with innumerable foci in the bone system together with diabetes insipidus, disturbance of growth and roentgenographic changes in the lungs. In several cases where the disease commenced as a solitary granuloma, continued observation has

revealed additional foci, so that in our material the number of foci increases with the length of the observation period.

3. *Morphologically* transitions were demonstrated from the lipoid-free «eosinophil granuloma» through granuloma with beginning lipoid phagocytosis with Touton cells to entirely xanthomatous tissue.

4. After this, the concept «eosinophil granuloma» can no longer be maintained as a nosological entity but has to be considered a not altogether infrequent clinical monosymptomatic form of Schüller-Christian's disease that often heals without becoming generalized.

5. Complete agreement is demonstrated between the various histological pictures in the cases of «eosinophil granuloma» here described and the various histogenetic phases of Schüller-Christian's disease that may be characterized as follows:

1. The hyperplastic-proliferative phase.
2. The granuloma phase.
3. The xanthoma phase.
4. The fibrous (or healing) phase.

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Electrocardiographic Observations during intravenous Injection of Acetyl Choline.

By

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During the work with acetyl choline shock treatment of schizophrène patients in the Settlement of «Philadelphia» we have had an opportunity to investigate the effect of larger and smaller doses of acetyl choline on the heart and circulation, among other things as it appears electrocardiographically seen.

Already years ago the effect of acetyl choline on the heart and the circulation generally has been the subject of mentioning in the literature (Hunt and Taveau 1906, Dale 1914). Electrocardiographic observations after intravenous doses in human beings on the other hand have only been stated by a few authors, first Podomoro 1932, later Carmichael and Fraser, Nielsen and Trier, Serena and others. As the results obtained by us in certain points deviate from and in other points support the publications of these authors, and thus the question still seems to contain problems, the present statement may perhaps count on interest.

Hunt and Taveau in 1906 demonstrated, that acetyl choline injected into the circulation of mammals has a strong depressive effect. Later on Dale pointed out, that the effect of acetyl choline very nearly corresponds to the effect brought about by a stimulation of the parasympathetic nerves; after an intravenous dose the

blood pressure decreases and a reduction in the frequency of the heart action appears. This inhibitory effect only endures for a few seconds and is followed by an increase in the blood pressure and the frequency to above the original ones. The vasodilation still persists after the inhibition of the frequency has stopped. The reaction may be reproduced at any time. Injected into the vasomotoric system the acetyl choline is almost immediately hydrolysed by the specific esterase present everywhere in blood and tissue.

Carmichael and Fraser (1933) have by intravenous injections in human beings confirmed Dale's animal experiments regarding the reduction of the heart frequency and fall in blood pressure and has shown, that this holds good both of the systolic and the diastolic blood pressure. Also in human beings the effect is of a very brief duration, in the experiments in question a few seconds, and is followed by a rise in the blood pressure and an increase in the frequency. The effect of a certain dose varied in different test persons, and might entirely fail to appear after a previous injection of atropin, on the other hand not after a previous injection of adrenalin. Eserin intensified the effect and protracted it somewhat.

The doses used in the works reported here and in other works towards human beings must be characterized as moderate ones. The effect of large intravenous doses, thus as the substance is employed for acetyl choline treatment ad modum Fiamberti has been described by Fiamberti and by Waal and in a previous report from the Settlement of «Philadelphia» (Poort and Stigaard: «On the Treatment of Schizophrenia with Acetyl Choline Shock»). The effect corresponds in all essentials to a universal parasympathetic irritation, but is, however, complexically composed, as also distinct sympathetic reactions appear, which may be connected with the fact, that the impulse from many sympathetic nerve fibres are conducted by means of acetyl choline, not «sympatin». Of typical sympathetic phenomena may thus be mentioned contraction of the pilomotor cells («goose flesh»).

Also as regards the parasympathetic innervation of the heart and the effect of acetyl choline on it, there is the difference, at any rate on dogs and cats, as stated by Goldenberg and Rothberger, that the sinus rhythm in these animals is far more easily affected by doses of acetyl choline than by irritation of the vagus. Acetyl

choline doses, which were able to cause stagnation of the atriums, profound conductivity disturbances in them or auricular fibrillation and complete interruption of the conductor on the atrio-ventricular border, had only an inconsiderable effect on the sinus rhythm. However, it must be remembered, that there is a quantitative difference in the irritation of the right and the left vagus, as the right one in warm-blooded beings shows a strongly negative chronotropia, which is quite missing in the left one. There seems to be a tolerable agreement between the effect on the heart by irritation of the left vagus and by doses of acetyl choline.

In certain cases the 2 vegetative nerve systems alternate in preponderance during the expansion of the effect, thus for instance both as to the blood pressure and the frequency, where after a previous fall in both cases is seen a rise in the values, which are often placed higher than the original ones; this is probably due to a reflex effect via sin. carotic. or the root of aorta.

The fact that an intravenous dose of acetyl choline thus is not identical with an universal parasympathetic irritation is quite clear and demonstrated both by elder and younger authors (Hunt, Carmichael and Fraser, Goldenberg and Rothberger, Waal, Poort and Stigaard). This of course does not exclude, that the acetyl choline and »the vagus substance» are identical, possibly chemical substances, which are very closely related to each other.

The fact, that the idea of intravenous injection of large doses of acetyl choline to human beings for a long time caused heavy misgivings, was probably due to the fear of a fatal heart stoppage, eventually permanent damage to the myocardium. The state of the heart caused by larger doses must also be characterized as a quite unphysiological state, principally different from the normal diastole of the heart. The main difference is, that the coronary circulation under the effect of the acetyl choline in such doses is suspended, while at the same time the intracellular assimilatoric and dissimilatoric processes are continuing in a more or less altered shape. As appears from the acetyl choline shock treatment this state is tolerated surprisingly well, at any rate within certain limits. According to about 5,000 acetyl choline shocks with a total stoppage of the heart for $\frac{1}{2}$ —1 minute reported in the literature, the heart

action (and the respiration) has every time promptly and spontaneously returned except in one single case reported by Waal, where artificial breathing had to be given for some time. The doses employed for acetyl choline shocks are as mentioned rather high in comparison to these mentioned in the works cited above; maximally we have here in the settlement of «Philadelphia» reached to 1.0 g intravenously.

During the shock treatment we have seen, that the pulse a few seconds after a suitable dose becomes insensible to the touch, the heart action (the respiration possibly too) seems to have been totally suspended. The fact, that the heart (and the diaphragm) are really put out of function, is demonstrated by Waal by x-ray transillumination of the thorax during the shock. The blood pressure, both the systolic and the diastolic one, falls quickly, and soon they are immeasurable by the ordinary stethoscopic judgment on account of the cessation of the beat of the pulse. We have made no attempt to measure directly the pressure in the arteries. When the blood pressure after the return of the heart action again is controllable, it is strongly decreased, the systolic one reduced by 30—60 mm hg, the diastolic one often below 30 mm hg. Both the systolic and the diastolic action, however, have a strong tendency to rise to normal values or to values, which are often 2—4 minutes after the attack placed 10—20 % higher than the habitual one. A couple of examples:

	years	dose	habitually	before inject.	after							
					1 min.	1 ½	2	3	4	5	6	12
H. B.	50	0.7	115/75	140/80	110/55		130/70	130/70	130/70	120/75	120/75	110/7
E. N.	33	0.7	120/80	130/80	70/40	100/50	100/50	100/55	105/60	105/70	115/75	
M. W.	31	0.1	100/60	120/80	100/45	110/50	100/65	100/70	105/70	100/65	100/70	110/6

The electrocardiographic changes after giving of acetyl choline to animals have been investigated among others by Lueken and Schütz and Goldenberg and Rothberger. The former in working with frog's hearts found, that the acetyl choline effect shortens the circuit of action strongly; the change is spontaneously reversible.

Goldenberg and Rothberger, who have made thorough animal experiments, demonstrated in dogs as the first appearing change a weakening of the auricular contraction and a corresponding typical change in the P-wave of the electrocardiogram. By larger doses an auriculo-ventricular block and conductionary disturbances in the atrium appeared, while the sinus rhythm was scarcely affected. Still larger doses caused auricular fibrillations. No weakening of the contraction of the ventricle appeared; on the other hand suppression of the formation of irritants in the atrio-ventricular node, so that by an auriculo-ventricular block a ventricular standstill might arise. After cutting through the bundle of His (or both branches) the automatical ventricular rhythm became somewhat slower. The initial complex of the electrocardiogram remained unchanged, on the other hand a depression of the S-T segment was seen. — In cats and dogs no suppression in the formation of excitation in the atrio-ventricular nodus, so that one by a complete auriculo-ventricular block now and then had the possibility of interference between the sinus rhythm and the more slow auriculo-ventricular rhythm (interference dissociation). This shows, that the place of the block is above the source of the impulse in the auriculo-ventricular node. Towards the atrium muscle stripes acetyl choline was found to have an at any rate preponderatingly negative inotrop effect, to a smaller degree a negative chronotrop effect. On isolated heart — lung preparations from dog acetyl choline caused a reduction in the volumen per minute.

Electrocardiographic investigations of the effect of acetyl choline on human beings seem first to have been made by Pomodoro (1932), who demonstrated changes in the cardiac rate; in patients with circulatory affections, further lengthening of the P-R, atrio-ventricular block and protracted suspension of the sinus rhythm. Several authors have found flattening of the T-wave and shortening of the relative Q-T duration. Nielsen and Trier by the relatively small doses of 15—35 mg intravenously obtained bradycardia, a relative shortening of Q-T, flattening of P in lead II and III (in case of pronounced bradycardia, otherwise not), no changes in T or P-Q.

Arturo Serena, who, just as we, has occupied himself with electrocardiographic investigations during acetyl choline shock treatment ad modum Fiamberti, has taken electrocardiograms partly

in connection with the individual shocks, partly before and after a more protracted shock cycle, in most cases consisting of 40—50 individual treatments. He points out the difficulties connected with taking of electrocardiograms after giving of substances, which, as for instance acetyl choline, cause more or less unrest in the muscles, possibly spasms. Even after smaller doses of acetyl choline disturbances are often appearing in the curve on account of coughing, which unfortunately appears at a time immediately after injection of the dose, when the look of the electrocardiogram is particularly interesting. The author points out the analogy existing between strong acetyl choline effect and Morgagni-Adam-Stoke's syndrome: in both cases appear unconsciousness, cessation of respiration and muscular spasms, when the standstill of the ventricle has exceeded a certain time limit, and in both cases these symptoms disappear as soon as the action of the ventricle starts again. The reduction in the cardiac rate was dependent upon the size of the dose and the rate by which it is injected into the venous system.

As the purpose of Serena's work was to demonstrate possible damage to the myocardium caused by the acetyl choline, the author before the cure has examined the electrocardiogram at rest in the three extremity leads and one chest lead; further continuous registration in lead II both in cases, which only appeared as »*burasca vascolare*» (vascular »storm») i.e. cases without loss of consciousness and without muscular spasms as well as fully developed shocks; the recording is not concluded until the normal cardiac rate has been restored. Further electrocardiogram has been taken every 2 minute in all extremity leads for the first 25 minutes after the conclusion of the shock. Finally rest-electrocardiograms has as mentioned earlier been taken after the conclusion of the whole shock cycle.

Altogether 13 of the patients have been watched in this manner. The investigations showed, that the electrocardiograms at most 16 minutes after the stoppage of the muscle spasms is again completely normal, both as to sinus impulse, duration of the atrio-ventricular conduction, the P-Q segment, the look of the initial complex, the S-T segment and the terminal deflection. Inversion of the T-waves has never been observed, neither during the shocks nor afterwards. In some cases the S-T was depressed for some

minutes, however, not to such a degree, that any importance might be attributed to it. After small acetyl choline doses, which only caused »burrasca», the electrocardiogram has been normal in the course of at most 5 minutes. After a complete shock cycle the electrocardiogram has shown no changes that might be attributed to the treatment, that means that the recordings before and after the treatment have been identical.

In the same manner Waal had taken an electrocardiogram a few times before and after the acetyl choline shocks and has found no permanent changes. Even when the collapse seemed to be catastrophic, the electrocardiogram has shown no anomalies afterwards.

Own observations.

For those a Siemens — Einkoffer electrocardiograph has been employed. The patients have always been placed in a lying position during the registration. Acetyl choline »Roche» in dry ampullæ of 0.1 g have been used. The substance has been dissolved in 1 or 2 ml of sterile water, out of regard to the speedy destruction the solution has been produced immediately before the use. The injection has been made in an elbow vene as quickly as possible, and with a view to the esterase activity care has been taken not to aspirate more blood into the syringe than absolutely necessary in order to secure the intravenous placing of the canula.

1. Acetyl choline in doses causing no shock.

Figure 1 shows electrocardiogram, lead II from 19 years old man, N.O., who before this had a normal electrocardiogram, action 90 (psychic tachycardia). 0.08 g of acetyl choline has been given dissolved in 1 ml water. This is a dose which was unable to cause any shock in this patient, but large enough to show the effect of acetyl choline on the heart action (»burrasca vascolare»). 9.3 seconds after the injection appeared, as shown by the curve, rather suddenly a reduction in the rate of the heart to pronounced bradycardia, in which QRS are normal as before the injection, the P-waves somewhat lower, the T-waves somewhat higher. During 5—6 seconds the rate evenly works itself up to the normal level.

Of practical reasons the curve cannot be shown in full extension; instead a reduced diagram is included (about 1:4), in which the R-waves are indicated.

Altogether 20 such experiments have been made on 13 patients, which did not previously offer any clinical signs of morbus cordis, and whose rest-electrocardiograms registered immediately before were normal except in three cases, where they offered left axis deviation (2 cases) and Wolff, Parkinson and White's syndrome. Lead II has been used, in a single case, however, lead I. 5 minutes after the dose one has taken a new rest-electrocardiogram in 3 extremity-leads; in 4 cases at the beginning of the series of experiments this, however, was omitted. Doses from 0.05 to 0.18 g of acetyl choline were employed.

The effect obtained from a certain dose was different from one patient to another. In the individual patient the effect was dependent upon the size of the dose. In 5 cases (in 3 patients) no electrocardiographic changes were seen. The rest-electrocardiograms of these patients did not otherwise offer any typologic common features.

In the cases, when inhibition of the cardiac rate appeared, this set in 2.2—22.3 seconds after the injection and endured for 5.2—41.0 seconds, often followed by a briefly lasting tachycardia.

In the bradycardic stage (15 cases) the curves have shown the P-waves in 10 cases more flat, in 5 cases unchanged as before the dose. The P-Q duration unchanged, the T-waves in 10 cases higher in 1 case lower, in the remainder of the cases unchanged.

In the tachycardic stage (in the 12 cases, where such ones appeared) the P-waves in 6 cases were more flat, never higher, P-Q of normal length except in 1 case, where a shortening appeared, the T-waves in 5 cases higher, in 3 cases lower, in 4 cases unchanged.

Measuring of the relative Q-T (calculated after the formula of Larsen and Skulason) has given strongly varying results, the formula may probably only be employable within certain upper and lower frequency limits. The QRS complex has in most cases been unchanged as to duration and the size of the individual waves. In a few takings, however, the R-waves have varied somewhat in size as they have been both greater and smaller, without conformity to any law having asserted itself. The S-waves have likewise been

of a slightly varying size. These changes in QRS have constantly been within the limits of the normal. In a single record with short-lived bradycardia appeared quite isolated a punctual, but in shape strongly deviating, low »striding» initial* complex of the duration of 0.13 seconds, preceded by normal P-wave and normal P-Q-distance. Such conductionary disturbances in the ventricles without any previous deviation in the conduction of the atriums have also been found in the later experiments but otherwise they are a rare phenomenon. The S-T segments have in all cases had a normal appearance.

In 5 cases the bradycardia has been divided into parts by an intermediary section with a quicker action up to the frequency of 70 (compensatory sympathetic effect, released from sin. carot. or the root of aorta?).

In 1 case appeared somewhat later in the tachycardian stage first tri- and diphasic, then purely negative T-waves (lead II); the change appeared to be of a transitory nature and was not accompanied by subjective or objective inconveniences from the heart. As regards the cause of such transitory negative T_2 -waves the same considerations must be made, I suppose, as mentioned by Nørskov in a very similar work on the electrocardiographic changes after metrazol shocks, namely that the negativity may be due to 1) coronary insufficiency e.g. on account of anoxemia, low blood pressure or spasms, 2) preponderance of the sympathetic; after Nordenfeldt's and other's opinion preponderance of the sympathetic may be able to cause this change. That the sympathetic is preponderating may among other things be seen from the tachycardia, which in this case was rather pronounced.

In 2 cases (0.1 and 0.2 g of acetyl choline in the same patient) a shortlived total block was seen for 4—6 seconds with a complete suppression of all activity of the ventricle, so that only the isolated P-waves are to be seen; in one of the cases appeared afterwards arrhythmias and a few extrasystoles of ventricular or atrio-ventricular origin; in the other case the block was concluded by a few strongly deformed ventricular complexes. In these electrocardiograms appeared a few times 1—3 supernumerary P-waves as a preliminary of auricular fluttering.

In 1 case the frequency fell from 80 to 16, increased a little, but

then went over to auricular fibrillation with rather quick irregular ventricular rate, which continued for more than 25 minutes after the injection; by registering 2 days later (the patient had left in the meantime) the electrocardiogram was again as before the experiment.

In patients with Wolff, Parkinson and White's syndrome heightened and lengthened T_2 waves appeared during the bradycardia, either with two humps or with plateau formation at the top. The P-Q conduction time was unchanged; QRS (lead II) which originally lasted for 0.14—0.16 seconds and had no independent Q- and S-waves was shortened to 0.09 seconds with small positive Q- and S-waves.

In the other 14 cases, in which electrocardiograms have been registered 5 minutes after the injection, this has been normal.

In these cases there has been no question of muscular spasms or unconsciousness; any pronounced pallor of the skin has not appeared, on the other hand a strong hyperemia particularly in the face with a subjective feeling of heat a couple of minutes after the time, when the cardiac phenomena had played themselves out.

II. Electrocardiogram during a completely developed shock.

On 4 schizophrene patients without any sign of heart affection continuous electrocardiograms, lead II, have been taken 11 times before, during and a little after the fully developed shock. In 1 case the conduction time in the rest-electrocardiogram, however, was 0.23 seconds. Doses from 0.1 to 0.7 g of acetyl choline have been used intravenously.

After a latent time of 1.4—1.7 seconds a short retardation has occurred in the cardiac rate, and then a complete standstill of the heart action, which measured on electrocardiogram lasted for 14.5—37.1 seconds. Under this the patient has been totally unconscious, in most cases the respiration was suspended for 10—20 seconds.

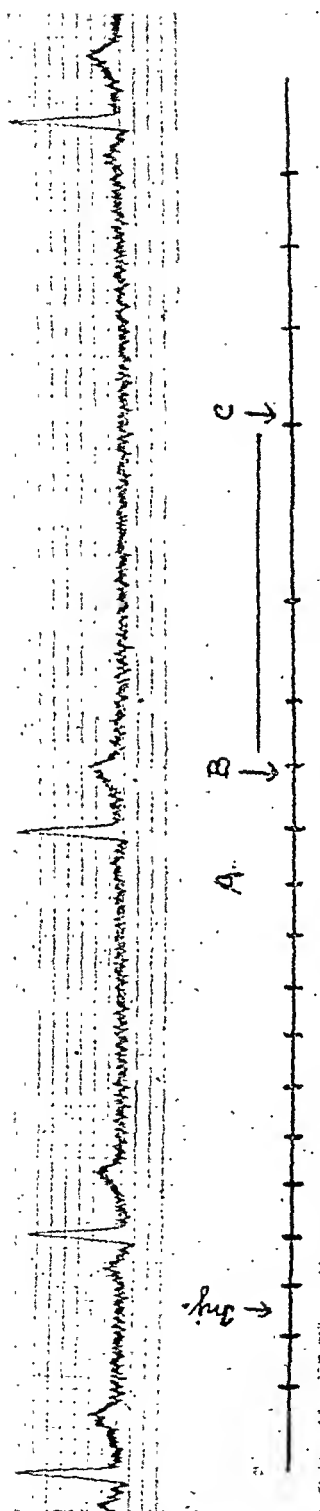
After the pause the heart action always commenced again spontaneously; often first by a single beat with intervals of seconds, but with evenly rising frequency, as mentioned previously, often to values placed a little above the original ones.

In the bradycardic stage the P-waves have been more flat or diphasic or unchanged or have been missing (a-v-rhythm), the P-Q prolonged or unchanged, the T-waves *in all cases higher*; Q-T in 6 cases out of 11 shortened, in 2 cases lengthened, in other cases unchanged. S-T-segments in 4 cases lightly depressed, in other cases unchanged. The R-waves often lightly heightened and somewhat varying.

In the tachycardic stage (in 7 cases, where such ones appeared) the P-waves in 3 cases have been more flat, in 3 cases unchanged, in 1 case there was auricular fibrillation. P-Q shortened in 5 cases even very considerably, in 1 case unchanged, in 1 case there was auricular fibrillation; the T-wave was in 6 out of the 7 cases heightened, in 1 case unchanged. Q-T relatively lengthened (after Larsen and Skulason's formula) in all 7 cases; S-T-segment in 3 cases out of 7 slightly depressed, in 4 cases unchanged. Figure II shows electrocardiogram before and after the shock.

In 6 cases, whereof 5 cases originating from the same patient, an a-v-rhythm regularly appeared after the pause, in 1 case with transition to auricular fibrillation; in another case some extrasystoles appeared, in a third case coupled extrasystoles. In 1 case from another patient the curve offered temporarily only regular P-waves in a low rate after the pause with a complete suppression of the impulse to the ventricles. In 1 case a couple of regular complexes appeared in the middle of the pause at intervals of 1.4 seconds. In 1 case the action, just after the standstill of the heart, was slightly arrhythmic.

In 10 cases rest-electrocardiograms have been taken 10, 15 or 20 minutes after the attack; these records have offered no abnormality and on the whole had the same appearance as the electrocardiograms before the attacks, however, P₃ was in 3 cases respectively isoelectric, diphasic and of changing appearance, but positive — before the attacks in all 3 cases normal. T₃ in 2 cases diphasic, in 1 negative against previously normal. In 1 case the electrocardiogram has been watched every ½ hour for 2 hours after the attack; 1 hour after it a temporary diphasic T₃ appeared, otherwise the curves have been like those before the attack.



In the diagram the R-waves are traced. The injections have been given at the time stated. At A the diastole commences to be lengthened quite faintly. The piece of B—C corresponds to the electrocardiogram given. Marking of time: 0.05 seconds.

Fig. I.



before shock

after shock

Fig. II

III. The electrocardiogram before and after the shock cycle.

In 21 schizophrene patients in the age of 17 to 56 years, who have been exposed to a more protracted acetyl choline shock cycle (17 have recieved 15 fully developed shocks each of them, 4 respectively 24, 13, 10 and 6) electrocardiographic examinations have been made before the cycle (in 2 cases, however, it had to be excluded on account of unrest; the electrocardiograms were normal after the treatment in these 2 cases) and some time after their conclusion, most often for 14 days, with a view to a more protracted possibly at a later stage appearing changes. In the treatment doses of up to 1.0 g acetyl choline has been used intravenously.

Before the treatment the 14 electrocardiograms were normal, 2 showed left axis deviation, 1 offered Wolff Parkinson and White's syndrome, 1 had small excursions in all leads (below 0.5 mm) 1 too high R_2 and R_3 (0.25 and 0.20 respectively); no one of the 21 patients had any clinical signs of heart affection. All patients tolerated the cure well, did not at any time offer any signs of affection of the heart of the circulation, neither after the conclusion of the cure.

At the examination of the patients after the treatment the electrocardiograms of the 15 patients were like those before it; the electrocardiograms with too high R-waves had become normal. In 3 cases the P-Q was lengthened and above, what is permissible (0.25, 0.25 and 0.26 seconds respectively); in the control registration taken 2—3 months later it appeared, that this anomaly had disappeared. The electrocardiogram, which offered Wolff, Parkinson and White's syndrome was quite unchanged after the cure.

If the results of the 3 series of experiments are compared, one must agree to Serena's proposition — even if this researcher's investigations are chiefly of a negative nature — that the large doses employed in the acetyl choline treatment do not cause any permanent changes in the electrocardiogram, to say nothing of damage to the myocardium.

In contrast to this author and in agreement with many others (Pomodoro, Landau, Nielsen and Trier and others) it has been proved by our experiments, that the substance is able to alter the

electrocardiogram, on the whole as it might be expected, when taking for granted, that the effect of acetyl choline just as the effect of the vagus is preponderatingly localized to the atriums. Nearly all authors agree with regard to the bradycardia and the flattening of the P-waves likewise that the initial complex of the electrocardiogram is of normal appearance. Less agreement with the authors mentioned have we found with regard to the Q-T-duration and the S-T-segment, and in complete contrast to all the authors cited we have found the *hightening of the P-wave at the bradycardiac stage to be a phenomenon that is practically constant*. The cause of this latter disagreement may probably be sought for in the fact, that we have used far larger doses. Likewise in contrast to most authors we have proved, that in many cases in human beings — as demonstrated previously in animals — complicated disturbances of the conduction appear during the passage of the impulse through the conducting system; thus there may also in human beings appear complete suppression of the impulse in the atrio-ventricular nodus or appear abnormal «pacemakers», at other times so severe conducting disturbances in the atrium, that they manifest themselves in auricular fibrillation with rather quick heart action. Even in our comparatively sparse material we, as appears from the above, have seen many examples of such disturbances.

Of course it must be deliberated, whether the changes found are primary effects of the acetyl choline or — wholly or partly — may be secondary ones, caused by myocardial anoxemia, which probably to some degree arise during the standstill of the heart, and which at any rate hardly can be abolished by the tachycardia, which often appears, and during which the demand for oxygen of the myocardium is increased. As anoxemic changes are usually described (Lepeschkin): Tachycardia, hightening of P_2 , lowering of P-Q in lead II, flattening of T_1 , inversion of T_2 and T_3 and depression of the S-T-segment; P-Q is stated of varying duration, during extreme anoxemia in most cases shortened. In the bradycardic section of our curves, which certainly represent the proper and uncompensated effect of the acetyl choline, these symptoms have only appeared quite sporadically; depression of the S-T-segment in 4 out of 26 cases and lessening of the T-wave in 1 out of 26 cases; shortened relative Q-T-duration has been found somewhat

frequently, however, look at the previous remarks about that. Certainly it cannot be excluded, that the changes may be due to an anoxemic state of the myocardium, but after all it must be emphasised, that they have only appeared in a few cases, except the shortened relative Q-T-duration, which may rather be attributed to the extreme bradycardia. In the tachycardic states of the curves a shortened P-Q has appeared in 7 out of 19 cases and 3 times a depression of the T-waves has been seen, which symptoms coincide with the anoxemic ones and which are possibly also due to anoxemia. Altogether it is still not the electrocardiographic characteristics of the anoxemia which put their mark on the picture, one gets after administering of acetyl choline.

Our material seemed further to show, that while the sensibility to acetyl choline in the different hearts examined is very varying, there is a tendency to the effect, that the individual heart again and again reacts against acetyl choline with the identical electrocardiographic — and thereby functional — changes. It seems to be an obvious supposition, that the sympathetic — parasympathetic adjustment («tonus»), which a heart in advance is subject to, and the stability of this «tonus» to a high degree is determining the nature and the degree of the change caused by an acetyl choline injection.

Summary.

A review of literature is given concerning the effect of acetyl choline on heart and circulation. Attention is drawn to the difference between stimulation of the parasympathetic nerve system and the effect of intravenous acetyl choline injection.

Electrocardiographical investigations previously made are mentioned and my own enclosed. In connection with the acetyl choline shock a.m. Fiamberti the following have been made:

1. a serie of electrocardiographical tracings in connection with injections of smaller not shockproducing doses
2. continued tracings before, during and after the injection of greater shockproducing doses
3. tracings before and after a larger shockepisode.

It may be confirmed that the acetyl choline shocktreatment a.m. Fiamberti does not seem to cause permanent changes of

the electrocardiogram, nor permanent injuries of the myocardium.

Agreements and disagreements between observations made by former authors as to the changes of the electrocardiogram after acetyl choline injections are pointed out and discussed. Some of the deviations may be explained by the fact that the author has used considerably greater doses than most of the former investigators.

It seems obvious to the author to presume that the »Tonus» (sympathetical — parasympathetical) the heart already possesses and the stability of this »Tonus» is highly determining with regard to nature and extent of the changes caused by an injection of acetyl choline.

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The production of the acute phase protein after nonspecific stimulation.¹

By

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History.

Löfström (1) recently described a substance which occurs under certain circumstances in human serum and causes nonspecific capsular swelling and agglutination of pneumococci. A similar substance may be obtained from rabbit serum. Human serum reacts best with type 27 and rabbit serum with type 16. Löfström (1) has suggested the term «nonspecific capsular swelling substance, or type 27 reactive substance». The reaction is seldom as intense as that occurring in specific capsular swelling, but it is nevertheless always readily distinguishable under the microscope. Löfström (2) later identified his substance with the acute phase protein, whose reaction with the C polysaccharide of the pneumococcus was described in 1930 by Tillet and Francis (3).

The reaction is carried out by Neufeld's method, which is used for type determinations of pneumococci. The amount of type 27 reactive substance is measured by titration by a method proposed by Löfström (1). A constant amount of serum is titrated on a slide against increasing concentrations of bacteria. The lowest density of bacteria is called no. 1 and the corresponding quantity of reactive substance in the serum is called titer 1. By a progressive doubling of the bacterial concentration in density 1, den-

¹ The expenses of this investigation were defrayed in part by a grant from Aktiebolaget Astra, Södertälje, Sweden.

mals. The amount of substance in the serum reached its maximum on the second day after the injection and had disappeared by the fourth day. A total of 18 injections was given over a period of four months. Although the maximum dose was kept the same, the titer for the substance gradually decreased.

Sulphur.

Approximately the same results were obtained when Sulfosin¹ was used (fig. 2). Five rabbits were tested, the starting dose being 0.5 ml, and the maximum dose 1 ml per Kg of body weight. Type 16 reactive substance was produced in all five animals after injection of the maximum dose. In only one animal was the titer as high as 16. After repeated treatments with the constant dose the titer decreased but the reduction was not so great as in the manganese experiments. Sixteen injections were given over a period of three and one-half months.

Gold salt.

The compound used, Aurothion Astra² was injected into five rabbits. The starting dose, 0.25 g was administered at intervals of two to three days, five times in succession. It caused a positive reaction in two animals, with titers of 1 and 2 respectively, following all the injections except the first. After the fifth injection one animal, which had shown a negative reaction, died for some unknown reason. After the 0.5 g dose type 16 reactive substance was produced in three rabbits, the respective titers ranging between 4 and 16. One of the animals showed a negative reaction during the entire treatment. No reduction in the titer occurred under continuous treatment, which was carried on for two and one-half months. Ten injections were given during this period.

Another gold preparation, Solganal³ was given to five rabbits five times, 0.25 ml at each injection. Thus, in this case, the dose was not increased during the experiment. The highest titer obtained was 4, this figure being observed in two animals. In three instances there was no reaction.

¹ Sulfosin Leo: Sulphur sublimatum steril 0.01 g/ml.

² Aurothion Astra: a combination of sodium gold thiosulfate and sodium thiosulfate containing 9.8 per cent Au.

³ Solganal (Schering): A disodium salt of sulfomethylaminoortoauromerkap-tobenzolsulfonacid. 36.5 % Au.

*Copper salt.*¹

The first dose was 1 mg, and the highest 32 mg. The 16 mg dose was given twice. The number of injections was 7, over a period of one and one-half months. Only one animal responded to the doses of 2 and 4 mg with a positive reaction, showing a titer of 1. After 16 mg the reaction in three animals was still negative and in the two others the titers were 4 and 2 respectively. After an injection of 32 mg the results were three positive reactions, with titers of 4, 2 and 1 respectively, and two negative. Thus, two animals did not react at all during the experiment. The animal showing a positive reaction to a dose as low as 2 mg also proved to be the most sensitive in respect of the higher doses of 16 and 32 mg, yielding a titer of 4 for these.

Sterile milk.

The starting dose was 0.5 ml, in response to which only two animals reacted, with titers of 1 and 2 respectively. When the dose was doubled the respective titers were 8, 4, and 2 in three rabbits while two showed no reaction. All the animals reacted to the 2 ml dose, the highest titers being 8 for one animal, 4 for two, and 2 for two. A remarkable feature was that the milk caused the maximum reaction the first day after the injection, while with the other substances tested this occurred on the second day. A total of 10 injections was given during two months.

*Omnadin*² (Bayer).

This preparation evoked no capsular swelling substance. Five animals were submitted to tests. The starting dose was 0.25 ml. The 1 ml dose, and the highest dose of 2 ml were both given twice each. The total number of injections was thus 6, and the experiment time one month.

Blood.

No reaction was produced in three rabbits from blood (10 ml) obtained by heart puncture and injected directly into a muscle. The experiments were repeated three times. Nor was there any result from defibrinated blood chilled to +4 C.

¹ Sodium salt of cuproallylthioacabamidbenzoic acid. Cu 18.5 %.

² *Omnadin* (Bayer): A mixture of protein substances, bile lipoids, and animal fats.

Experiments on human beings.

Manganese, sulphur, and typhoid vaccine, among other preparations, were tested on man for their power to produce Löfström's substance. Serum was examined each day in order to ascertain the content of type 27 reactive substance, and as a rule this was continued until the reaction present became negative. The majority of the injections was intramuscular.

The manganese salt in the form of Psorimangan was given to a patient suffering from an ordinary gastric ulcer, and also to seven patients with chronic primary polyarthritis.

The patient with the gastric ulcer was a woman, 37 years of age. The guaiac test on faeces gave negative results during her entire stay in the hospital, and no symptoms occurred after the injections (fig. 3).

The first three patients (fig. 4 a, b, c) suffering from chronic primary polyarthritis had no capsular swelling substance in the blood before the treatment with the manganese salt. Arthritis patients per se, however, not infrequently show a positive capsular swelling reaction. Cases d and e are examples of this. In case f it will be seen that type 27 reactive substance was elicited by the manganese salt at first, and that after repeated injections, which were also given intravenously, the reaction became negative. Sulphur, given as Sulfošin, then induced the formation of the substance again, and the organism's power to produce it on sulphur stimulation did not diminish or disappear, while the manganese salt, when again administered (on March 31), still had no effect. This feature, viz. the reduction in the titer, and the often total disappearance of the reaction for a period of varying length after a pro-

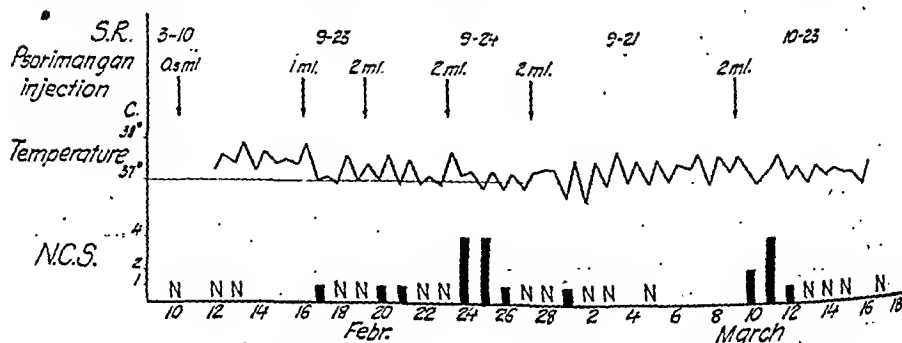


Fig. 3. Case 691/43. Gastric ulcer. Woman of 37 years. N.C.S. = nonspecific capsular swelling substance. S. R. = sedimentation rate in mm/1-2 hours.

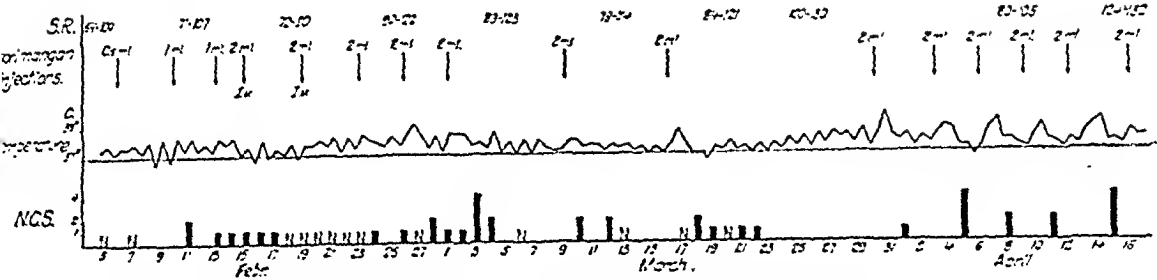


Fig. 4. a) Case 838/43. Chronic polyarthritis. Woman of 35 years.

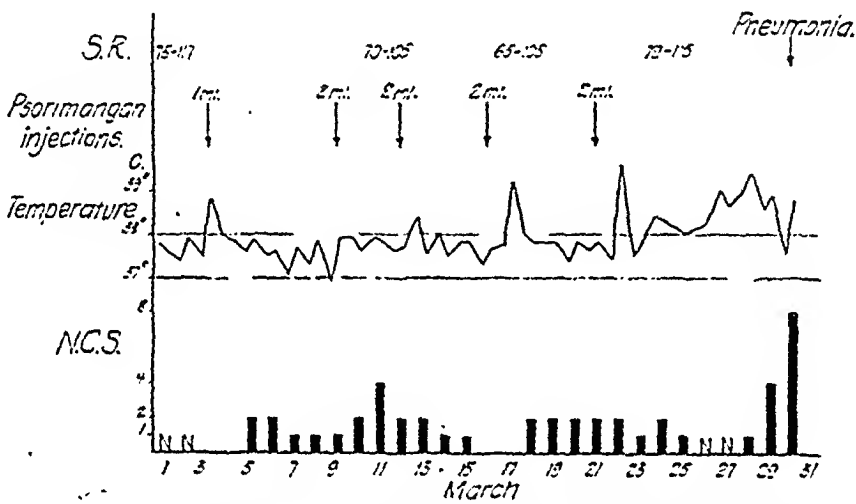


Fig. 4. b) Case 1347/43. Chronic polyarthritis. Woman of 55 years.

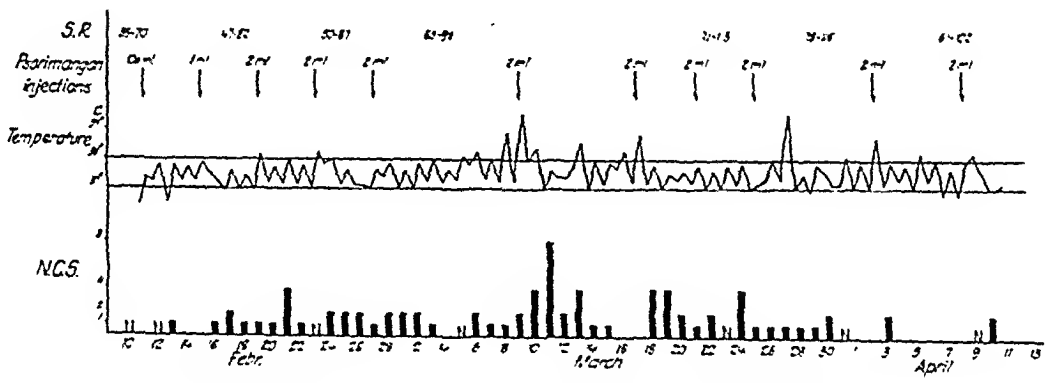


Fig. 4. c) Case 954/43. Chronic polyarthritis. Woman of 59 years.

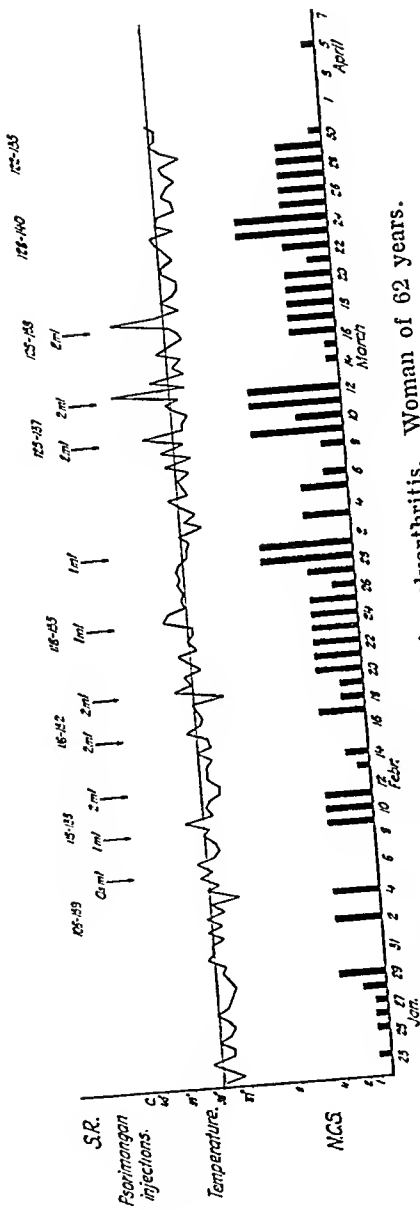


Fig. 4. d) Case 69/43. Chronic polyarthrit. Woman of 62 years.

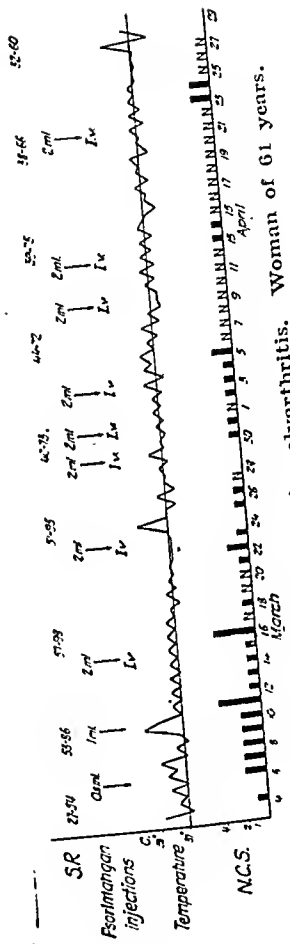


Fig. 4. c) Case 1452/43. Chronic polyarthrit. Woman of 61 years.

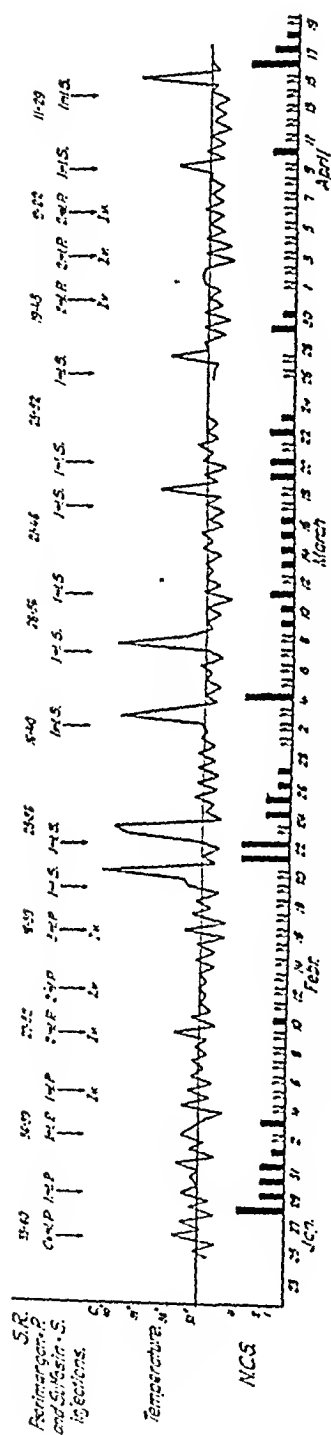


Fig. 4. f) Case 7367/42. Chronic polyarthrit. Man of 32 years.

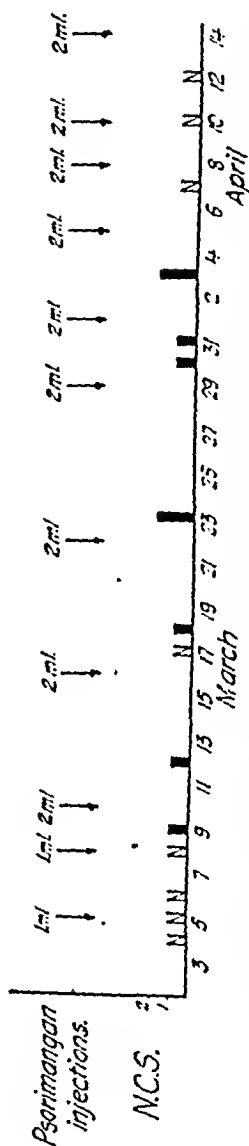


Fig. 4. g) Chronic polyarthrit. Woman of 50 years. Given manganese salt injections in the Out-Patient Dept. All injections intramuscular, except for a few given intravenously (I. v.). N.C.S. = nonspecific capsular swelling substance. S.R. = sedimentation rate in mm/1—2 hours.

Table.

Patient (Record no.)	S.R.	Previous treatment (Year)	Investigation on N.C.S. ¹ Feb. 20.			
			Gold treatment. Occurrence of N.C.S. after gold injections given:			No gold treatment Occurrence of N.C.S.
			Before 16/2	16/2	18/2 or 19/2	
6	8	—40,—41		—		
9	36		+2			
11	58				+1	
22	35			—		
24	16	—41		—		
26	6			—		
27	41			—		
34	25				—	
35	61			—		
36	19	—41			—	
38	7	—38,—42			—	
41	8					—
47	10	—39,—41			—	
50	1					—
51	46				—	
56	31				—	
64					—	
74	11			—		
76	43				+1	
78	42			—		
80	25				+1	
84	52				—	
85	30			—		
86	20				+1	
87	62			—		
94	11	—36,—39,—40				—
112	70	—39,—40,—41		+4		
145	48	—42				—
146	37				—	
147	30					+1
162						—
168	52	Sept.—42			+2	
171	17	—36,—37,—42		+2		
173	90	—40,—41,—41			+2	

¹ N.C.S. = Nonspecific capsular swelling substance.

Patient (Record no)	S R	Previous treatment (Year)	Investigation on N.C.S ¹ , Feb. 20.			
			Gold treatment. Occurrence of N.C.S. after gold injections given:			No gold treatment Occurrence of N.C.S.
			Before 16/2	16/2	18/2 or 19/2	
174	31					—
183	16				—	
191	34					—
1108	12				—	
1110	50	—41			—	
1130	48	—42	—			
1135	36		—			
1157	20				—	
1178	12		—			
1180	39				+1	
1181	50	—35			—	
1187	10	—42,—43				—
1196	3	—42			—	
1212	24	—36,—38			—	
1227	29	—39,—41			+1	
1229	37			—		
1231	40	Aug.—42	+1			
1238	30				—	
1240	17		—			
1250	95	—41	—			
1251	10				—	
1255	16	—41,—42			—	
1258	17	—41,—42		—		
1259	10	—42			—	
1262	17	—41,—42			—	
1264	57			+1		
1272						+2
1273	11	—38,—42		—		
Total: 62			No. of patients given gold treatment: 52. Of these 13 showed a positive capsular swelling reaction.			No. of patients not given gold treat- ment: 10. Of these 2 showed a positive capsular swelling reaction.

+ 1 = positive capsular swelling reaction titer one.

chronic pneumonia) showed the same positive capsular swelling reaction before and after.

Iodbismol¹ Astra, which was given to a 56 year old woman with erythema induratum, produced no reaction. She received a total of 18 ml intramuscularly, in doses of 2 ml at two-day intervals.

Before *specific liver treatment* was started on an old woman suffering from pernicious anemia she was given both manganese (Psorimangan) and sulphur (Sulfosin), and she then showed normal reactions, with the formation of type 27 reactive substance (fig. 6). The reticulocytes at first increased in number, after the administration of Psorimangan, but remained at low values. After specific liver treatment (Heptomin Tika) a normal increase in reticulocytes occurred and no type 27 reactive substance was produced in the serum.

About 60 patients with chronic polyarthritis who were being treated at the Nynäs Sanatorium, and most of whom had received gold treatment, were submitted to one test (see table.). Out of 52 who had received gold injections (Aurothion Astra, Myoral Astra, Neosolganal Schering) on the days immediately preceding the experiment, in most instances not more than 4 days before, 13 showed a positive reaction. Ten were given no gold treatment and in 2 of these the reaction was positive. It is not certain whether the positive reactions were due to the gold injections, since as already stated, Löfström's substance is sometimes found in chronic polyarthritis.

Discussion.

The statements of Carlens and Löfström with regard to sulphur have been confirmed. Of the numerous agents said to be therapeutically effective in producing so-called nonspecific stimulation, or believed to act in such a manner, the following were tested on human beings: — A salt of manganese (Psorimangan), sulphur (Sulfosin), typhoid vaccine, and gold preparations. In rabbits, the effect of manganese salt (Psorimangan), sulphur (Sulfosin), gold salt (Aurothion, Solganal), milk, copper salt Astra, Omnadin Bayer,

¹ Iodbismol Astra: Sodium iodobismuthite, 6 per cent in ethylenglycol.

On the other hand, extensive changes, involving even the entire reticulo-endothelial system, may be found in the form of proliferative reticulosis. In the first place, this is evident from the autopsy findings in some cases of Schüller-Christian's disease — *e.g.*, Henschen's Case I, where reticulosis was demonstrated in the spleen and lymph nodes, and in Gerstel's case, in which proliferative reticulosis was seen in the lungs, liver, spleen and lymph nodes besides in the inconspicuous osseous foci. It is furthermore evident from our Case 5 where in the early stages of subsequently clinically typical Schüller-Christian's syndrome the bone marrow on sternal puncture showed 30 % atypical monoeytoid cells, while the blood showed a leukemoid picture with 14,700 leucocytes per cm^3 , 46 % of which consisted in the same large reticularells as seen in the bone marrow. This picture was so striking as to be suggestive of leukemic reticulosarcomatosis. Later on, however, these changes subsided and were replaced by periodical moderate eosinophilia.

How these changes and the splenomegaly occurring in rare cases of Schüller-Christian's disease are to be interpreted is difficult to decide and will not be discussed further here. But it is to be emphasized that these findings lend support to the view that the primary change in Schüller-Christian's disease is a proliferative reticulosis which thus appears to be more widespread in the organism than suggested by the limited osseous foci.

The histological features of the various stages from eosinophil granuloma to generalized typical Schüller-Christian's syndrome are plainly evident from the cases here reported (Figs. 1—9).

In addition, these histological pictures are particularly suitable to elucidate the histogenesis of the disease in the early stages. In reality it is practicable histologically to distinguish between four stages, although there need not be any sharp border between them. Thus the disease begins with an entirely 1) *hyperplastic proliferative phase* (*e.g.*, Cases 2 and 5, see Figs. 1, 2 and 8) with more or less diffuse reticulohistiocyte proliferation which — as observed, for instance, in Case 2 — is often associated with pronounced eosinophilia. In this stage the histological picture resembles a true reticulosis or reticulohistiocytosis and is liable to be mistaken for a tumor, especially reticulosarcoma (as in our Case 5). Gradually, however, this stage will be replaced by the 2) *granuloma phase* with granulomatous tissue (Case 4, see Fig. 5) with blood vessels and

negative despite renewed injections of manganese, but on the administration of sulphur the usual reaction was again produced.

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On the acoustic theory of percussion.

By

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It is a fairly common experience in acoustics that problems as to the behaviour of a system subjected to a single shock may be profitably treated by first considering how the system reacts to sinusoidal vibratory forces of different frequencies. Curiously enough, there seems to have been no attempt to treat even part of the percussion problem along such lines. All published theories of percussion seek to understand the very complex problem by reasoning from the behaviour of the body under the impact. Obviously the results should be the same independent of the way in which the analysis is made, provided it is made complete. However, in view of the great complexity of the body as an acoustic system no complete analysis has been possible. A highly important and very thorough study by Landes (1939) with modern apparatus is no exception. He has (quite consciously) made rather simplified assumptions regarding the force-time-curve of the impact, considering it to be rectangular in shape. Now, as will be shown, the form and duration of that curve is perhaps the most important variable in percussion which we can choose at will, and which can have an influence on the sensitivity of percussion as a diagnostic method. The kind of treatment adopted in the present study, while quite possibly unsuited for other aspects of the problem, brings this one out very clearly. Consequently there seemed to be justification

however, by a favourable arrangement of their phases, amplitudes and frequencies at a single given moment, they may also work together and then give a collected impulse. In point of fact it can be calculated for each arbitrary form of a force-time curve what frequencies, amplitudes and phases the vibrations must have in order to give the impulse when acting together. This is called calculating the »Fourier spectrum» of the impulse and curve 3 shows a hypothetical one which might belong to the impact in curve 2. This spectrum shows how much force of each frequency is contained in an impact of the form given in curve 2. If the force-time curve had been more angular, peaked and short, the spectrum would have contained relatively more of the higher frequencies; if the curve had been more extended and rounded the high frequencies would have been weaker and the low ones more predominant.¹

By an impact on the thoracic wall, then, we administer an infinite number of vibratory forces of different intensity and frequency. Each one of these forces gives rise to a sound. The magnitude of the vibratory forces is determined by the impact's Fourier spectrum (curve 3) and the resulting loudness for given magnitude of force by the frequency-response curve 1. Consequently, the loudness received by the ear at each frequency will be the product of curves 1 and 3, something like curve 4, which may be called the loudness spectrum of the impact. (This derivation of curve 4 is simplified. See below.)

We are now ready for the synthesis. The task of percussion is to demonstrate changes in or under the thoracic wall, either from place to place, from moment to moment, or from person to person. These changes always affect the frequency-response curve 1. They may do this either by affecting the stiffness of the wall directly under the place of impact, or by affecting the »travelling possibilities» of the vibrations. The changes may in principle be supposed to affect the conditions similarly for all frequencies: this is, however, an improbable possibility. It is much more likely that they have different importance for different frequency regions. The changes

¹ Landes (1939) has shown that the impacts are not always simple but may be repetitive, at least under the conditions of his experiments. We can, however, confine ourselves to the analysis of the simple impact, as the repetitive one provides us with nothing fundamentally new.

in or under the thoracic wall may also affect the temporal course of the impact, particularly in percussion without a pleximeter. The resulting change of the impact's Fourier spectrum is nevertheless in all likelihood of altogether secondary importance as compared with the changes in the frequency-response curve. The changes in the impact's loudness spectrum, curve 4, which give rise to the changes in the apprehended percussion sound, will therefore be located at the same frequency regions as the changes in the frequency-response curve 1, and will be primarily determined by these. *Thus, what percussion ultimately shows, are changes in the frequency-response curve.*

Now, one of the aims of this article is to maintain that improvements in percussion technique should be possible by improving the form of the impact. This will be clear from the following considerations.

The observer behind the ear does not, after all, apprehend the loudness spectrum of the impact as an extended curve but as the short sound phenomenon it actually is, all at once. Therefore, his attention will be mainly caught by the most prominent, that is, the loudest, parts of the loudness spectrum. It is also clear that changes in these frequency regions will be more easily detected than changes in less prominent regions of the impact's spectrum. Now, generally, the physiological and pathological changes in the frequency response curve of the thorax will be more or less concentrated to «regions of maximal change». Obviously, then, changes in the thorax will be most easily detected if the regions of maximal change of the frequency response curve of the thorax coincide with the regions of maximal loudness of the impact's loudness spectrum. Thus, the effectivity of percussion will depend upon the possibilities of adjusting the loudness spectrum of the impact to the acoustics of the problem in hand.

If, in different conditions, the same frequency region were always affected it should be possible to develop a generally optimal impact. It seems more probable, however, that different frequency regions are interesting in different connections. It is thinkable that a certain change in the thorax, e.g. a pleural exudate, primarily affects the conditions for the low frequencies. Percussion should then be performed with long and rounded blows. It is not at all certain that the form of impact supplied by the usual

finger-finger percussion is optimal. If it were too angular and pointed the situation might conceivably be improved by so simple a measure as turning the pleximeter finger and striking on the volar side. The curve of the blow will be even rounder in percussion without a pleximeter, direct on the soft parts.

In other situations the thoracic conditions are perhaps most changed for the high frequencies. Here, then, one should try for short, peaked curves which are obtained by letting small, hard objects strike against one another. Use of percussion hammer and bone pleximeter, or the coin-test, belong to this category. A certain variation in finger-finger percussion is already obtained by varying the method of striking the plexor finger or the pressure of the pleximeter finger.

In order to simplify the argument, we have hitherto assumed that loudness is directly proportional to physical sound pressure. This is not true — the relation is more complex. Moreover, if in a composite sound the *physical intensity* of all the notes rises equally, the *loudness* of the low notes rises considerably more than that of the high ones: the loudness-intensity curve of the low tones is much steeper. These facts have no great importance for the theory as developed so far. They give rise to a certain dependence of the form of the frequency-response curve on the level of exciting intensity and cause the true loudness spectrum of the impact to differ somewhat from the product of curves 1 and 3. But the main interest of the loudness-intensity curves of the ear is that they probably explain most of the differences in results between forceful and gentle percussion¹.

It seems extremely likely that the proportion between the physical intensity of the different frequencies generated is but slightly changed by the force of the impact. The relative importance of superficial and deep structures for the acoustic behaviour of the

¹ The proper way of obtaining the loudness spectrum for the impact is: A frequency-response curve with sound pressure (instead of loudness) as the ordinate is multiplied by the Fourier spectrum of the impact. The product curve is transferred point by point into a loudness spectrum by reference to published curves relating physical sound pressure at different frequencies to subjective loudness. The resulting loudness spectrum of the impact will differ in scale but not very much in general shape from that derived by the incorrect method described above.

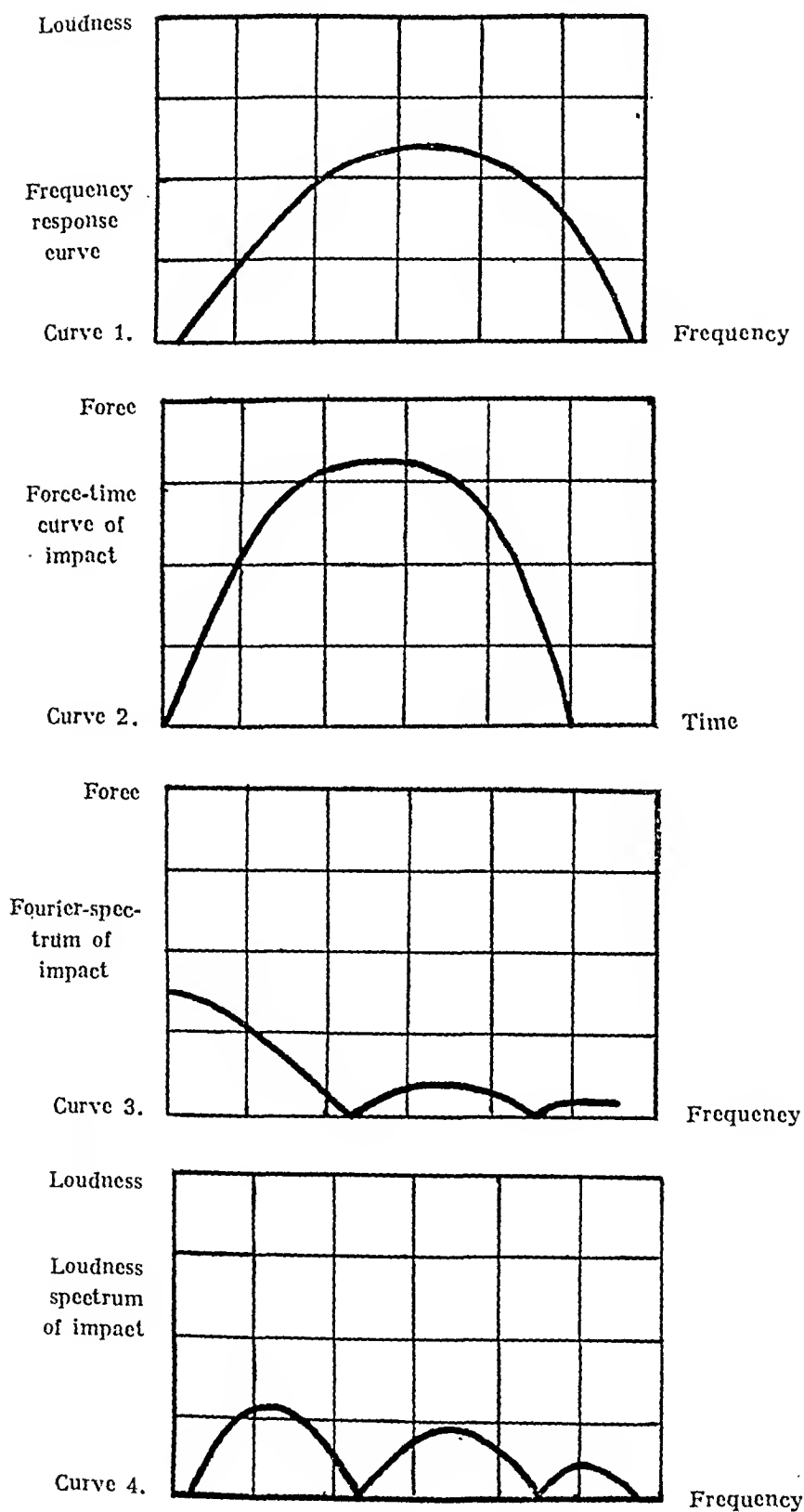


Fig. 1.

thoracic wall — and only the vibrations of that we hear — should not be very dependent on the intensity of acoustic excitation. Thus, the often expressed belief that intensive percussion is needed for bringing the deeper structures into play does not seem reasonable from our point of view. On the other hand, the quality of the percussion sound is dependent on the intensity of the blow and the reason for this is, that, at high intensities, the loudness of the lower tones is relatively enhanced, while at low intensities the low notes are the first to disappear. Which of the two alternatives is most suitable will depend on the problem in hand.

In the course of time a great many percussion methods have been published, varying in respect of finger position, pleximeters, and similar details. What differentiated them most, physically speaking, was probably the force-time-curve of the resulting impact. These many suggestions have nevertheless appeared at random, and not as the result of a systematic search for the frequency regions in which the most interesting changes are to be found. The nearest approximation to such a study seems to be the work of Bass (1935). This author used tuned metal pleximeters and showed that in different situations different tuning was advantageous.

Perhaps even better results could be obtained by substituting vibrators of suitable frequencies for the impact. It would then be possible to stimulate selectively with the interesting frequency. Attempts along this line have been made with tuning-forks (e. g. Vernieuwe 1926) and electromagnetic devices. (Bock 1924). The failure of such methods to become more developed and universally accepted may be due to the view that any acoustic device is inferior to X-rays. Even those, however, who do not share this pessimistic attitude probably consider the simplicity of percussion to be its main factor of merit. Therefore, a future development of percussion will probably sooner concern methods of obtaining suitable impacts than methods using more or less complicated apparatus.

Summary.

The relations between the acoustic properties of the thorax, the Fourier spectrum of the percussion impact and the loudness spectrum of the resulting percussion sound are discussed. The importance of matching the Fourier spectrum of the impact to the acoustics of the thorax is pointed out.

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Accumulated cases of chronic benzene poisoning in the rubber industry.

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(Submitted for publication May 2, 1944).

Hitherto, chronic benzene poisoning has not received the same attention in Sweden as in certain other countries, particularly Germany, France and U.S.A. This is no doubt mainly due to the fact that benzene has not been very extensively used in Swedish industry. The blockade of the last few years, with the attendant difficulties of importing the appropriate solvents of normal times has meant that benzene has been used more and more as a substitute, primarily for benzine. Nevertheless, benzene has also been used earlier on in Sweden, and has caused cases of chronic poisoning. During the years 1937—1939 the State Insurance Office compensated 27 cases, but not later than the years 1940 and 1941 there was a distinct increase by 12 and 18 cases respectively. The increased number of cases must often be ascribed to the fact that the management and the workmen do not know how poisonous benzene is, and further, that in many cases the output has been intensified and carried on in unhygienic premises. A particular

This subject has recently been dealt with in this journal by Stenstam, who goes through the literature and describes one case of his own. The author therefore refers to this paper as regards chemistry, path. anatomy etc., and also the bibliography.

instance of this is the frequently entire lack of ventilation. Some of these causes lie behind the cases of poisoning to be dealt with in this paper.

Benzene has a high toxicity in air. The degree of risk depends on the susceptibility of the individual, the length of exposure, and the concentration in the air. On this account it is difficult to determine the danger limit. Bowditch and Elkins give the desirable concentration of benzene in the working premises as under 0.24 mgm/l air. All the same these authors have two cases where the patients were affected at a lower concentration. Flury considers it should not exceed 0.1 mg/l air, and Hunter says the only safe concentration is 0. Plainly, benzene is a dangerous poison, and the literature contains numerous cases of poisoning with high morbidity and high mortality. (See Stenstam).

A factory in South Sweden manufactures rubber raincoats. The work is done on a conveyor belt, with alternate sewing and gumming. This latter was mainly done by hand on open tables with a solution of 10 % rubber in 90-degree benzene. The solution was kept in open tins. Before the different gummed pieces were ready to be put together, practically all the benzene would have evaporated, this latter process taking a minute or so. When the factory was working at full capacity about 50 kg of benzene would evaporate in the 8 ½ hours going to the normal working-day. The workroom had a capacity of about 3000 m³. There was no mechanical ventilation before the cases of poisoning appeared. If the amount of evaporated benzene be evenly distributed over the premises, it gives a concentration of about 17 mg/l air — in other words, a tremendous amount. The girls stand direct over the garments and will therefore be exposed to an even higher concentration. When Statens' institut för folkhälsan (the State Institute of Public Health) instituted inspections of the air conditions, the cases of poisoning had lowered the number of workers to a third of the normal figure. The individual working capacity had also declined. It was calculated that about 8 kg benzene were now being used per 8 ½ hours, as against the former 50 kg. The air conditions had also been improved by powerful fans, which sent in about 100,000 m³ of fresh air in 8 ½ hours. In spite of this, air analyses made by Civilingeniör Erik Thrysin showed a benzene content of 0.44—0.70 mg/l air. As is evident, the workers had been subjected

to a very intensive exposure to benzene, in spite of the powerful fans and low working capacity.

When the cases of poisoning were discovered, protective measures were at once taken on the initiative of the State Institute of Public Health (through Civiling. Erik Thrysin and med. lic. Kuno Quarnå). The system of fans was expanded, the work-tables were covered in and provided with individual ventilation, the tins of gum were reconstructed so as to make the evaporation surface less. After these steps had been taken, new air analyses were made, in which no benzene could be demonstrated in the samples. A more detailed description of the steps taken and of the results obtained is given by Thrysin. The continued clinical control of the workers also show these steps to have been effective, since there were no fresh cases and the general state of health was raised.

At the beginning of 1942 attention was drawn to the conditions in the factory. Even before this, however, the employees had complained of the disagreeable smell of the gum, and of obstinate headaches and tiredness. Some of them had also been to different doctors, who sometimes found them anaemic or diagnosed nervousness. It was only after a few serious cases had been admitted to the Medical Department of the Borås Central Hospital that chronic benzene poisoning was diagnosed.

The series of different measures then instituted included a medical examination of all the 184 workers (169 women and 15 men). Of these, 60 (i.e. 32.6 %) were then or later entered on the sick-list as suffering from chronic benzene poisoning: 58 were women, 2 men. The large number of poisoning cases can be explained by a forcing of the work by the installation of conveyor belts, with increased consumption of benzene, and the fact that this was done before the proper ventilation had been arranged for. 24 cases have been in hospital for a longer or shorter period. In July 1943 — after 16 months — 12 are still on the sick-list, 46 have been written off as healthy, and 2 are dead. These figures clearly show the serious character of the poisoning. All those on the sick-list have received compensation in accordance with the legal regulations as to insurance against occupational diseases.

An account will here be given of the results of the examinations made on the workers placed on the sick-list. When these examinations began there was great anxiety among the workers, and it

Table 1. The invalids' subjective troubles.

	Number of cases	%
Headache	41	72
Tiredness	50	88
Vertigo, nervousness, somnolence, insomnia	19	
Shortness of breath, palpitation	8	
Gastric trouble, nausea, vomiting	13	
Cutaneous hemorrhages	25	44
Bleeding of the gums	7	
Deranged menses	7	
Loss of weight	9	
Paresthesia	12	
Skin changes	5	
Benzene taste	2	
Smarting of the eyes	8	

was necessary to make a preliminary examination of them all as quickly as possible, and weed out the affected. The hurry, lack of personnel, etc., meant that in many cases this could not be as thorough as one might wish. Gradually, however, attempts have been made to complement the examinations as much as circumstances permitted.

The *subjective symptoms* are very varied. They are hardly noticeable at first, and can easily be mistaken if the possibility of benzene poisoning is not borne in mind. Table 1 shows the commonest subjective discomforts of the patients. 73 % had headaches. This proved to be very obstinate, and persisted for a long time even after the blood changes had considerably improved. Tiredness was the commonest symptom, appearing in 88.5 %. This, too, was excessively obstinate. The patients suffer from it months after improvement in other respects. They complain that they cannot take even short walks, and that they have to lie down even very simple household jobs. Signs of an increased tendency to bleed are common. 48.5 % of the patients had cutaneous hemorrhages, appearing mainly on legs and arms, seldom on the body. These are often large and spreading, to begin with; they appear without demonstrable trauma. A gentle pinch can give hemorrhages the size of a child's palm. They are also usual in cases where there are

no noticeable signs of bleeding tendency or vascular brittleness (lack of vitamin C). They often persist month after month; a number of patients still have them after a year on the sick-list. By that time they have usually become smaller disappear more rapidly, and do not appear so often. Other abnormal hemorrhages are those of gums and nose, as also derangement of the menses (irregular, sometimes more frequent and copious menses). These troubles appear only among those with more serious blood changes: only in two cases were they so severe as to call for local treatment. In no case has a gynecologist needed to intervene. Nervousness, vertigo, somnolence or sleeplessness, shortness of breath and palpitations are other common troubles. Gastric trouble of a dyspeptic nature, nausea, vomiting and loss of appetite appear in 21.5 %. In a number of these cases it was impossible to exclude gastritis; it is a moot point whether benzene has anything to do with its onset. An interesting symptom in this connection was shown by two cases, who complained of a benzene taste in the mouth. Schrenk and others have shown in experiments on animals that inhaled benzene is secreted in the stomach. This may be the cause of the gastric troubles and the benzene taste. Skin changes have manifested themselves in the form of itching, possibly with pruriginous papules or slight dermatitic changes. There was loss of weight in 9 cases, some extremely marked — up to 10 kg in one year. Paresthesia usually appeared in the form of prickings in arms and legs. No objective derangements of sensibility or other neurological symptoms could be demonstrated. 8 complained of smarting in the eyes. These displayed at most a slight conjunctival redness. This symptom is, incidentally, very common among factory-workers, and may have other causes than benzene.

This symptomatology agrees on the whole with the one given in the literature. It is, however, important to realize clearly that the objective findings are in no way correlated with the subjective symptoms. According to Greenburg these latter are not so very important and may be absent even in serious cases, a fact also confirmed by this material.

Mignolet puts as heading to the description of the blood changes of chronic benzene poisoning: *Le benzol, poison du sang*. He wants thereby to show at once the central importance of the blood changes for this disease. They have always attracted the greatest

interest, and as already Santesson (1897) drew attention to anemia and leukopenia. Later investigators have laid most stress on the injury to the blood-forming organs, which usually gives anemia

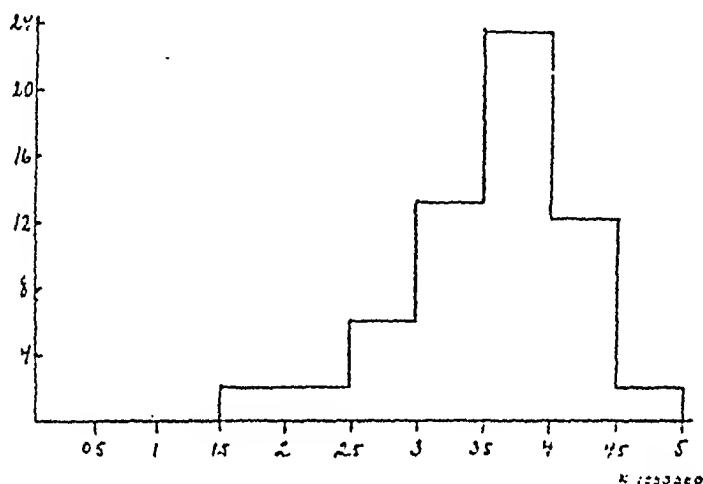


Fig. 1: Red blood corpuscles.

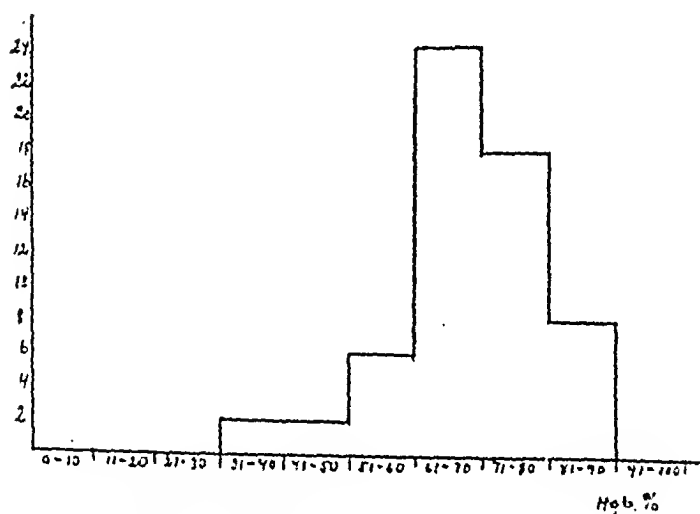


Fig. 2: Hemoglobin in % (Authenrieth).

ranging from hypoplastic to aplastic. In a number of cases, however, benzene can have a stimulating effect on the bone marrow, so that a hyperplasia sets in that can pass into genuine leukemia. These latter changes have not been observed in our cases. The most important changes in the blood are centred round the triad anemia, leukopenia, thrombocytopenia.

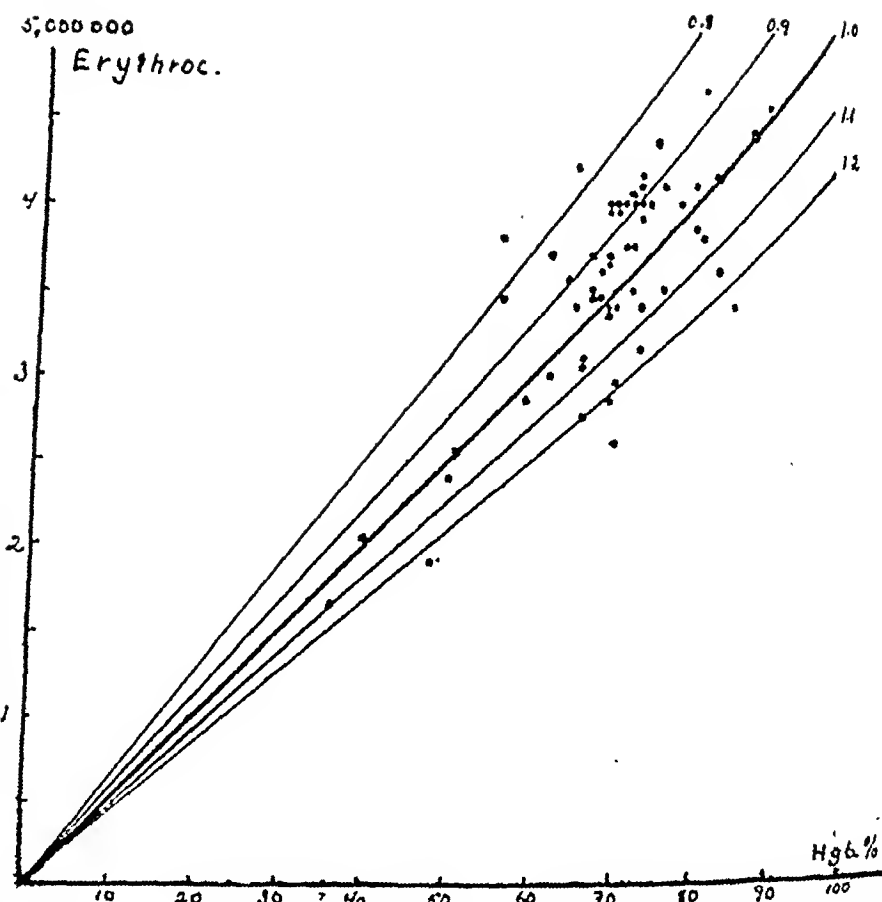


Fig. 3: Colour Index.

The *anemia* in this investigation has been moderate. The values for hemoglobin (determined according to Authenrieth) and red corpuscles are shown by figs. 1 and 2. 60—80 % for hemoglobin and 3.5—4.5 million for red corpuscles are the commonest figures. As can be seen, only a few had a more extreme anemia. The size of the corpuscles has been much discussed. Goldwater finds macrocytosis, Kahle normal corpuscles, Hunter small corpuscles. Mignolet finds a hypochromatic and a hyperchromatic picture with equal frequency in mild cases, whereas the serious cases are as a rule hyperchromatic. This agrees with our findings in the material presented here. Fig. 3 shows the colour index exhibiting a fairly good distribution of hypo- and hyperchromatic

cases, yet with a tendency towards hyperchromia in more pronounced anemia. It would probably be impossible to draw any diagnostic conclusions from the appearance or degree of the anemia in this material. Moderate anisocytosis is common; sometimes there is poikilocytosis and polychromasia, as a rule more pronounced in the cases with more serious changes. Not even in the most serious cases have immature forms appeared. One of those to point out benzene's stimulating effect on the formation of blood is Hunter, who has 7 cases with an increased number of red cor-

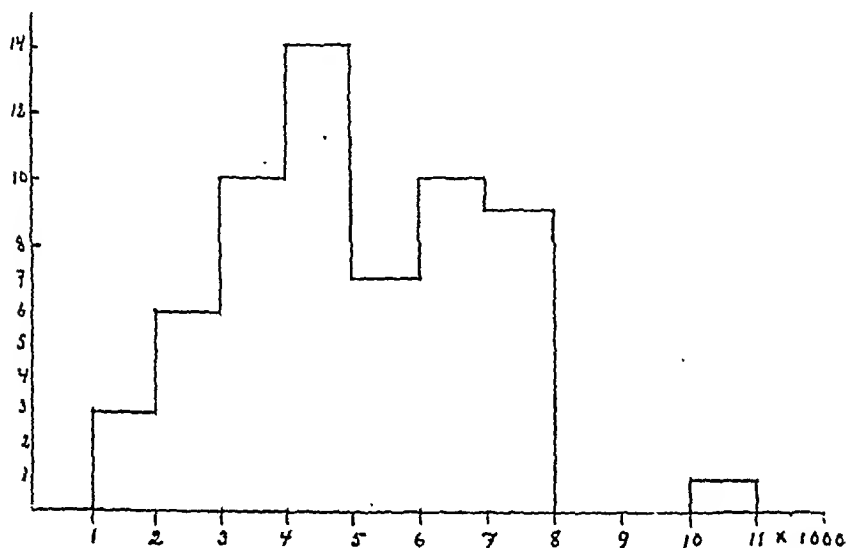


Fig. 4: White blood corpuscles.

puscles, and who considers that erythremia may be an early sign of benzene poisoning.

Ever since Selling's investigations *leukopenia* has been much discussed. There seems to be no relation between the anemia and the leukopenia, Greenburg and Mignolet consider the former to come earlier than the latter. The number of leukocytes is gradually shifted towards lower values, but the process is not very marked. Kahle finds leukopenia in only 30 %. The cases with raised leukocyte values are interesting. Hunter has several: one with up to 264,000 leukocytes. Erf and Rhodes have a patient with 137,000, mostly myelocytes — that is to say, pure leukaemia and with corresponding patho-anatomical findings. Fig. 4 shows the distribution of the leukocytes. Many cases lie within limits where

no certain conclusions can be drawn. Only 17 have values of less than 4000 per mm³; these were patients with pronounced anemia and thrombopenia. These values come from the first examination. The case histories below illustrate how the leukopenia can become more pronounced, and it will therefore be of great value when the sufferers are to be followed up.

It is primarily the granulated cells that diminish. The *differential count* will therefore be important. Nevertheless, Goldwater finds the lymphocyte percentage in his material to be about the same as in the control cases, and shows that there can normally be up to 60 % lymphocytes. A relative lymphocytosis occurs in the most serious cases in particular. Hunter finds a decrease of the granulated cells in the most serious cases, and takes this to be an early and important sign of poisoning. In this investigation the lymphocytes in the differential counts varied between 19 and 53.5 %, except in Case 5 where they were 86 %. Eosinophilia or basophilia was never pronounced, nor have any young or pathological forms appeared.

As one of benzene's points of attack is the blood-producing bone marrow, the *sternal punctures* in these cases have been studied pretty closely during the last years, and have increased our understanding of the patho-anatomical process. The changes in the blood prove to be a reflection of those in the bone marrow, which vary from severe hypoplasia to the most extreme hyperplasia with extra-medullary hematopoiesis.

However, the sternal puncture is not positive in all cases. Emile-Weil and others (1938) find a tendency to aplasia in only 73 %. Stenstam has discussed the findings at the puncturings in more detail.

Sternal punctures were made on a number of the cases admitted to the hospital. Docent Elsa Segerdahl, Upsala, has been kind enough to inspect the preparations. In no case did hyperplasia set in, and indeed, the examinations of the blood do not point in that direction, either. The preparations were all more or less poor in cells. The marrow of patients who otherwise have more pronounced subjective and objective symptoms is most often poor in cells. There are no abnormal cell forms in the erythropoiesis or leukopoiesis. The percentual composition falls within the normal limits, though there are as a rule quite a quantity of plasma cells.

One of the classic symptoms is *thrombocytopenia*, which has with justice attracted great interest. Goldwater and others have cases with 30,000 thrombocytes per mm^3 , and less. Greenburg and others find a distinct shift towards low values, and at less than 100,000/ mm^3 , the capillary weakness was increased in 23 of 26 cases. There are nevertheless severe cases without thrombocytopenia. Mignolet, Nikulina and Tetowa consider thrombocytopenia to be the first sign of chronic benzol poisoning.

In this investigation the thrombocytes have been calculated according to Kristenson. [Normal values are 200,000—400,000/

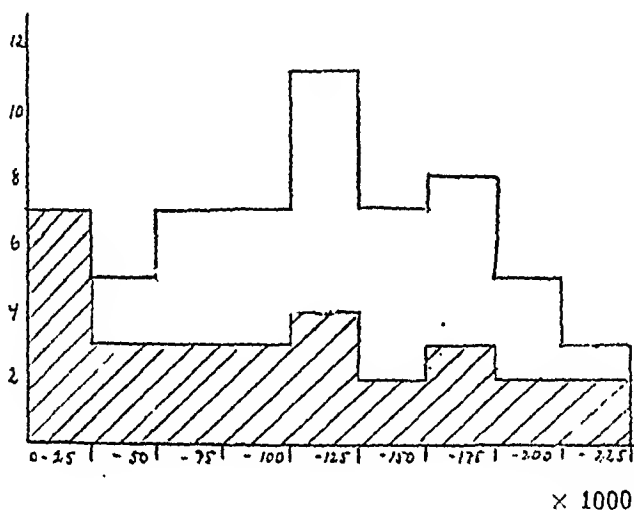


Fig. 5: Thrombocytes. The slanting lines give the number of patients with cutaneous hemorrhages in each group.

mm^3 .] Fig. 5 shows the results of the thrombocyte calculations. It is quite striking that an often particularly pronounced thrombocytopenia is found here. The values are much more pathological than for other blood investigations. None of the examined rubber workers with thrombocyte values of over 225,000/ mm^3 had had the disturbances, or blood values generally, to warrant a diagnosis of benzene poisoning. As a rule those with the lower values were most affected. The hemorrhages did not run parallel with the thrombocyte values. As fig. 5 shows, only those with values up to 25,000/ mm^3 all had hemorrhages. Above this figure, 22 had hemorrhages while 31 did not, with more or less even distribution in the different groups.

In this case the *prothrombin* determination did not arouse any

very great interest. Nevertheless Dawis speaks of prothrombin deficiency. Prothrombin determinations were carried out in 15 cases. Of these 6 had normal values; 4 a prolonged coagulation-time (Index < 100) and 5 a somewhat shortened one (Index > 100). There was no parallelism between the seriousness of the cases and the prothrombin determination; no conclusions can therefore be drawn.

The *bleeding-time* is usually reported as somewhat prolonged, yet according to Goldwater, not particularly marked. Greenburg et al. find it only in 5 cases of 105, Kahle on the other hand in 60 %. Mignolet finds cases with normal bleeding-time and low thrombocyte values, as also cases with long bleeding-time and normal values. Greenburg has had the same experiences. The bleeding-time has been determined in 28 of our cases. 18 had less than 5 minutes, 7 had 5—10 minutes, 3 between 10—15 minutes. Prolonged times appear only in those cases with more pronounced changes, particularly thrombocytopenia.

The *coagulation-time* is usually reported as prolonged. Mignolet quotes it as an early symptom, and an important one from a diagnostic point of view. Goldwater, however, finds it to be about the same as among the control subjects; Kahle finds it normal. Of 17 cases investigated for the coagulation-time, 15 showed it to fall within the normal limits of the method; only two cases were clearly prolonged (Nos. 4 and 5). And this in spite of the fact that the investigation was only carried out on more serious cases, who were being treated at the hospital.

Little attention has been paid in this connection to the *sedimentation rate*. Goldwater and Greenburg, with others, find it to be about the same as among the controls, but these authors have as a rule only examined less serious cases. Stenstam's case had 69 mm in one hour. Most authors do not mention the examination. We have found the sedimentation rate to be of a certain value. In many cases it is raised, in a number considerably so, often running fairly parallel with the seriousness of the case, and keeping obstinately high, only sinking on the general improvement of the patient. See the case histories.

Stasis tests (70 mm Hg in 5 mins.) were made in 34 cases, of which 28 were negative and 5 positive. Only in 3, who in addition had other pronounced changes, did any very large number of petechiae appear.

The diagnosis in an early stage of chronic benzene poisoning is often a very difficult matter. The anamnesis is of crucial importance. It is often necessary to go into the invalid's work in detail, and inquire into the solutions of this kind used there. That it is not always a foregone conclusion is illustrated by Hunter, who describes a telephone-girl who fell ill. It was only gradually discovered that she had for the last 6 years been wiping off her work-table with a cloth moistened with benzene. This little chronic dose gradually set up so serious a poisoning that she died. It is also important not to seek for the cause only in the patient's present work. The disease can also break out when the worker has given up his dangerous work — an important point as regards insurance. This was observed by Santesson, who assumed that certain changes are set up in the organism which, in a number of cases, take on a progressive character. In 4 of his cases skin bleedings did not appear until some days after the patients had stopped their dangerous employment. One of these died 5 weeks after having left the poisonous premises. Hunter has 2 cases who fell seriously ill as long as 15 and 18 months after they had given up their dangerous work. The delayed onset is often due to an infectious illness coming in between (Emile Weil and Hunter). Under ordinary circumstances the demands on the haematopoietic apparatus are moderate, but they are greatly increased in an infectious disease. Hunter draws an analogy with the insufficient heart, which can cope with the circulation in normal circumstances, but which fails on exertion. Hæctoen finds that benzene has an inhibitory effect on the formation of anti-bodies.

In most cases it is not possible to base the diagnosis on the subjective troubles; they are much too like those of general over-exertion and neurasthenia. The first time we went through the workers at this factory, a very large number complained of fatigue, headaches, etc. When the blood examinations gave them a clean bill of health, and the general uneasiness had subsided, they rapidly 'recovered'. The initial blood changes may also be such as not to allow of any definite pronouncement in many cases. Our investigation nevertheless points to the value of the thrombocyte determination. Pronounced anaemia without thrombopenia argues against benzene poisoning. The only certain is, often, to treat and keep the patient under observation. He is treated in the customary

manner, and no or only very slow improvement is obtained. To make a diagnosis of chronic benzene poisoning on someone who has been exposed to benzene is often taking too much for granted: simple secondary anaemia is a very common complaint, after all.

The course of the disease is extremely chronic. A sufferer has to rest, not for weeks but for months (Emile Weil 1940). Lamy et al. consider that the patient gradually gets better provided he escapes exposure to benzene. It is necessary to think of the length of the disease and the slowness in improvement. In spite of the treatment slight blood stigmata (mild anemia + leukopenia + neutropenia) are to be found after more than a year even in patients who seemed from the start to be only mildly affected, both clinically and hematologically. He also shows the danger of serious recurrence after a long period when the course was favourable: After 2 years there were still none of Mignolet's 26 cases with the normal number of thrombocytes or normal coagulation-time. Stodtmeister has a case which has been followed for 3 years. The blood values improved during the treatments (primarily blood transfusions), and remained good for a time, afterwards to sink anew, although the invalid was not working. This was repeated several times before his blood values finally remained at a respectable level. Bauer has followed one case closely. Not until after 5 months did the blood values begin to rise, but it took a further 2—3 months before they approached the normal. Stenstam's case needed 9 months for the hemoglobin and red corpuscles to become normal. The thrombocytes increase considerably more slowly for all investigators.

The long-drawn-out course is exhibited by this material, too. During the first 3 months 21 mild cases were written off as healthy, often such as had no very great subjective troubles and whose objective findings were so slight that there could be no risk in their resuming work. A number of these cases changed over to some other undangerous employment. During 3—6 months 14 further cases were written off, during 6—9 months 5, and during 9—16 months 6. 12 are still on the sick-list. Of these it should be possible to count on a number being able to recommence work relatively soon. A number, however, will assuredly need rest and treatment for a long time yet. Quarnå can not demonstrate any relation between the length of employment and the inability to work. Nor

does age seem to be of any dominating importance. A number of the more serious invalids have had a temperature of about 38°C , persisting for long periods. Case 4 had periods of subfebrile temperature during one year. In a number of cases the hemoglobin, erythrocytes and leukocytes decrease after the leaving off of work, even when the patients are treated at the hospital. Case 4 had on admission Hgb 51 %, red corpuscles 2.58 million, white corpuscles 1,700. 6 weeks later, despite Fe, Campolon and blood transfusions, she had Hgb 43 %, red corpuscles 1.95 million. The white corpuscles were 720 and, one week later, 580 mm/m³. The thrombocytes were relatively unchanged. See also Cases 3 and 5. Mignolet observed the same thing, and explained it by saying that there is for the moment no new formation of blood, the organism living on the circulating blood elements. Luckily no very serious complications have set in during the after-course in the form of complicating diseases. Case 3 shows that the body does not lack power to react with leukocytosis; while being treated in hospital the patient developed gangrenous appendicitis.

Regeneration takes place in this material in the same way as is generally reported in the literature. The hemoglobin and red corpuscles increase first; shortly afterwards come the leukocytes. The bleeding-time becomes normal in 1—2 months. The thrombocytes are most obstinate. They only rise very slowly, and after more than a year have still in many cases not exceeded 200,000, although hemoglobin, red corpuscles and leukocytes have long been normal, and the patient been without subjective discomfort. A number of earlier invalids, whose thrombocytes on the resumption of work were less than 200,000, have had no difficulty in managing, without new symptoms setting in.

It is also striking that the cutaneous hemorrhages obstinately persist, although no bleeding tendency can be discerned. To start with they are fairly large and widespread, but gradually begin to fade. They do not disappear altogether until many months after the other blood changes have subsided. Several patients returned to work in spite of the hemorrhages, and this could not be seen to hurt them. It was the most affected patients who usually had most hemorrhages, yet not without exception. A striking thing is that several cases of benzene poisoning, whose thrombocyte values had never been particularly low, nevertheless have large and obstinate

hemorrhages. As regards their duration, it has no connection with the thromboocyte values. Another singularly obstinate symptom is the tiredness. The patients complain that they are exhausted by even short walks or light household tasks. This symptom, too — which naturally, at any rate in part, may be purely psychic — persists for months, and many complain of it even after more than a year has elapsed since they were cut off from their work. No direct correlation between the tiredness and the objective findings has been found, nor has the tiredness stopped a number from being declared healthy and returning to work. In some cases it then improved noticeably, whereas some still feel a definite fatigue. No effect on the objective findings could be noticed in these cases.

In earlier stages it is as difficult to make a *prognosis*, as to foresee how long the disease is going to take. In all circumstances it is important to prepare the invalid for a long convalescence. During this time he lives protected in all ways from infection, with its increased demands on the myelogenic apparatus. When infections appear it is, naturally, often difficult to decide whether they are primary or whether they only found suitable soil in an organism with more or less impaired powers of reaction. The condition may get worse although the patient is treated in the best way. This is shown by Case 3, and by the two patients that died (Cases 1 and 2).

In the *treatment* it is most important that the invalid gets away from exposure to benzene, and is allowed to rest sufficiently long. This is without doubt the only thing on which everyone agrees. Otherwise, opinions are divided as to the merits of blood transfusions, injection with liver preparations, iron, arsenic, vitamin C. Other methods which have been attempted are injections of bone marrow, roentgen, splenectomy, etc. (See Stenstam). Certain authors predict good results from this, others none at all. Patients treated at this hospital have usually been given iron, heparforte, vitamin C and Campolon in large doses for months. In no case can any of these remedies be demonstrated to have had any effect whatsoever on the course of the disease. Blood transfusions have been given extensively. The immediate result is a rise of haemoglobin and red corpuscles, but after a few weeks they return to their earlier values. Consequently, the blood supply has only been increased temporarily. On the other hand there is a general

impression that the blood transfusions have an all-round strengthening effect. The patients feel livelier and more vigorous. The undoubtedly best and most effective therapy available at present is sufficiently long rest.

Certain authors think it would be dangerous for a sufferer from benzene poisoning to return to the work with this chemical on account of an acquired greater susceptibility to it. Dawis rejects this view; his opinion is that invalids recommence work before their myelogenic apparatus has been allowed to recover completely, this taking longer than the blood to become normal. Our experience is that, if the patients have been allowed a long enough rest from work, there is no danger in resuming it again, provided the hygienic arrangements and the control are satisfactory.

As in all work on occupational hygiene, the prophylactics are the most important element. Emile Weil says that no toxic substance makes for such great risks and is so impossible to protect oneself from as benzene in industry. It would therefore be best if it could be replaced by other, less dangerous chemicals. It was possible to do this in Belgium in 1936, and in certain industries in France in 1937. The results here proved fully satisfactory. Inspectors of occupational hygiene should have their eyes open to the risks of benzene. It is important to be especially on the alert when inspecting small workshops and the like. Perfect ventilation and no unnecessary evaporation of benzene from open vessels are pertinent requisites here. Similarly, the workers must be apprised of benzene's dangerous character. Underaged, pregnant or anaemic individuals must be barred from working with benzene. A medical examination before entering on such work, and subsequent control every 3rd—4th month, should be instituted. It should be possible to make these examinations extremely complete, if necessary, on account of the polymorphous picture that chronic benzene poisoning presents. The examinations must therefore not be mere routine, but each case examined and assessed separately. According to de Weerd, sternal puncture has no importance for the diagnosis of the mild cases. Here the changes were too small to allow of assessment. At the slightest sign of affection the invalid must be barred from the dangerous work sufficiently long for complete recovery.

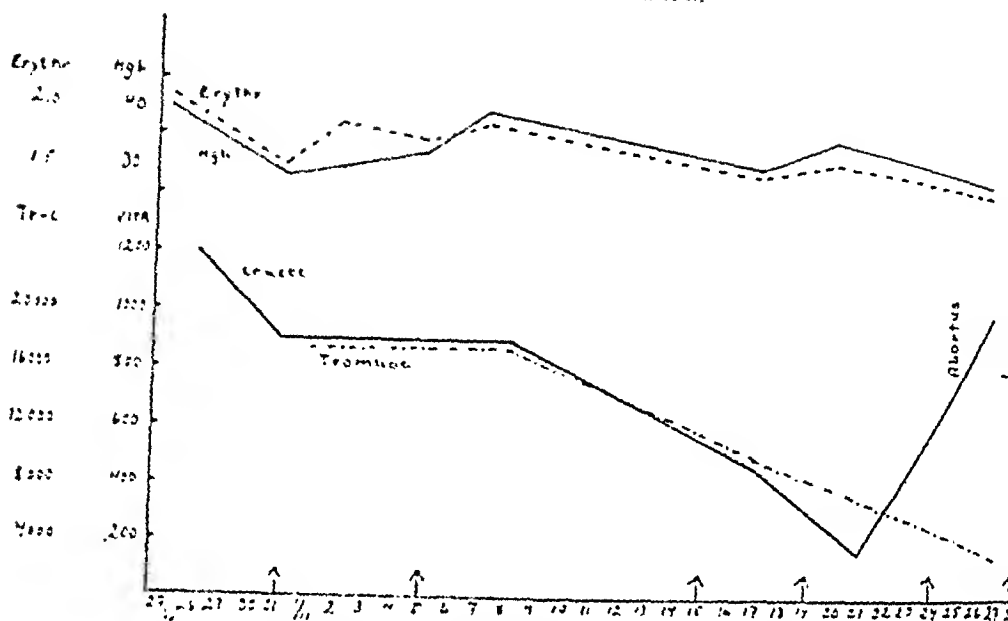


Fig. 6: Case 2. The arrows give blood transfusions.

Case 1.

Mattis J. 20 years. Case record: 2057/41.

In third month of pregnancy. Previously well. Some moderate nose bleedings the last 4 days before admission. Limp and tired. Came to Ear Dept. for nose bleedings.

Admitted 27/10 1941.

From the status: General condition not affected. Very pale. Mucosae pale. Fundus uteri level with umbilicus. Hb: 40 %. Red. corpuscles: 2.05 million. White corpuscles: 1,200.

Diff. count: Gran. 44.5 %, Eos 2 %, Lymph 44.5 %, Monoc. 9 %.

Thrombocytes: 18,000. Bleeding-time: 12 ½ minutes (normal time 2—4 mins.). Coagulation-time: 10 mins (normal: 5—9 mins.). SR: 35 mm/1 hour. The patient at first subfebrile; given several blood transfusions. Weber ++. Condition relatively good, apart from the lowered blood values. See fig. 6. On 25/11 her temperature rose to 39.4° C and she aborted without much bleeding. Bleedings appeared on the following days in conjunctiva, eye-grounds, urine, intestines, skin. Patient died 30/11, despite blood transfusions etc. Autopsy refused.

Case 2.

Ester E. 48 years. No. 367/42.

Previously well. Had worked at gumming for 3 months. Lost some weight in 2nd and 3rd months; troubled with shortness of breath. A few days before admission she began to get cutaneous hemorrhages, nose bleed-

ings, bleedings from the genitalia, continuing after admission to the Medical Dept. on 14/2 1942.

From the status: Hb: 69 %, red corpuscles: 2.86 million, white corpuscles: 5,700.

Diff. count: Gran. 75 %, Eos. 1 %, Lymph. 19 %, Monoc. 5 %.

Red corpuscles normal. Thrombocytes: 10,500. SR: 95 mm. Bleeding-time: 8 mins. Coagulation-time: 11 mins. Patient afebrile and unaffected until her temperature suddenly rose on 24/2 to 40.4°. General condition became very affected; consciousness lowered. Hb: 45 %, red corpuscles: 2.52 million. The white corpuscles dropped: 600—340—420. Thrombocytes: 3,000. She received repeated blood transfusions. In spite of this she got steadily worse, with bleedings in skin and conjunctiva. Died 27/2.

Autopsy. Pulmones: No free fluid in the pulmonary cavities. No adhesions.

Marked hypostasis in the dorsal parts. An abundance of subpleural bleedings in the form of dots over this area. Fairly abundant blood-stained mucosa in the bronchi. No signs of pneumonia.

Cor: Ordinary size, abundant pericardial fat. Scattered subpericardial bleedings in the form of dots. The endocardium also displayed these bleedings, though more sparsely. Otherwise nothing unusual in cardiac lumen, valvulae, ostia, myocardium or coronary vessels.

Hepar: Large, heavy, no subserous bleedings. Cut surface yellowish-white, resembling so-called reversed configuration.

Lien: Normal.

Renēs: Ordinary size and consistency. Abundant subcapillary bleedings up to $\frac{3}{4}$ inch in diameter. Hemorrhage foci up to the size of a pea in the parenchyma.

Stomach and intestines: Normal.

Preparations consisting of portions from liver, spleen, kidney, and bone marrow respectively were sent to the Radiopathological Institution, Professor O. Reuterwall, Karolinska Hospital, Stockholm.

Microscopic examination: A necrotic area, surrounded by a zone of hyperemic kidney tissue, was found in the kidney section at the boundary between medulla and cortex. In the centre of this necrotic area were several large clusters of Gram-positive cocci, without doubt staphylococci. The clusters in question were unquestionably of embolo-metastatic nature. The remaining tissue showed no noteworthy changes apart from hyperemia. The spleen section showed stasis and findings resembling those in infectious spleen. The liver section showed quite pronounced stasis and also fattiness in places. Otherwise no noteworthy changes. The bone marrow showed both fat-marrow and active marrow, without noteworthy changes in the cell picture.

Patho-anatomical diagnosis: Septic embolic focus in the kidney sample submitted + Stasis and hyperplasia in the spleen sample + Stasis in the liver sample.

Case 3.

Disa C. 34 years. No. 459—42.

Previously healthy. Increasing tiredness and shortness of breath during last 2—3 months. Vomited several times. The vomit smelt of benzene. Abundant bruises. Treated at the Medical Dept. 25/2—20/6 1942. From the status: Hb: 66 %, red corpuscles: 3.12 million, white: 2,500. Diff. count: Gran. 31 %, Eos. 2 %, Lymph. 51 %, Monoc. 11 %, Plasma cells 1 %. Thrombocytes: 15,000. SR: 34 mm/1 hour. Bleeding-time: 6 ¼ mins. Coagulation-time and prothrombin determination normal. Sternal punctate from 30/4 proved extremely poor in cells; otherwise nothing remarkable. — Temperature subfebrile to begin with. Patient given two blood transfusions. — 11/3 angina tons. with temp. 39.2° without effect on the blood values. 14/5 nausea, vomiting, abdominal pains downwards to the right. — Operation 14/5: Gangrenous appendix. After-course normal.

In connection with the falling ill of the patient the white corpuscles rose to 4,000, to drop again to 2,000 one week later. SR for the whole time was 20—25 mm. — After being discharged the patients improved very gradually, though still (June 1943) with cutaneous hemorrhages, headaches, tiredness. SR 7 mm. Can manage moderate work.

	Hb-%	red corp.	leucocytes.	thrombocytes
26/2—42	66	3,120,000	2,500	15,000
11/3—42	60	2,800,000	2,700	19,600
15/4—42	47	1,810,000	1,120	20,000
14/5—42	50	1,920,000	4,000	
22/5—42	49	2,140,000	2,800	34,000
8/9—42	83	3,540,000	3,800	142,000
23/3—43	93	3,900,000	5,200	132,000
1/6—43	98	4,000,000	5,000	138,000

Case 4.

Elsa J. 43 years. No. 501/42.

Previously well. Increasing tiredness and headaches during last 3 months. Cutaneous hemorrhages for last 2 months. Menses somewhat irregular and more copious recently.

Treated at the Medical Dept. 2/3—27/6, 21/10—14/11 1942, 1/4—4/5 1943. — On admission she was gray-white in the face, with abundant bruises on legs and arms. Her blood values are shown in fig. 7. Bleeding-time: 5 mins. Coagulation-time: 19 mins (normal: 2—5 mins.). SR: 67 mm. Diff. count: Gran. 53 %, Eos 2.5 %, Lymph. 27 %, Monoc. 16.5 %. Sternal punctate very poor in cells. Cells normal.

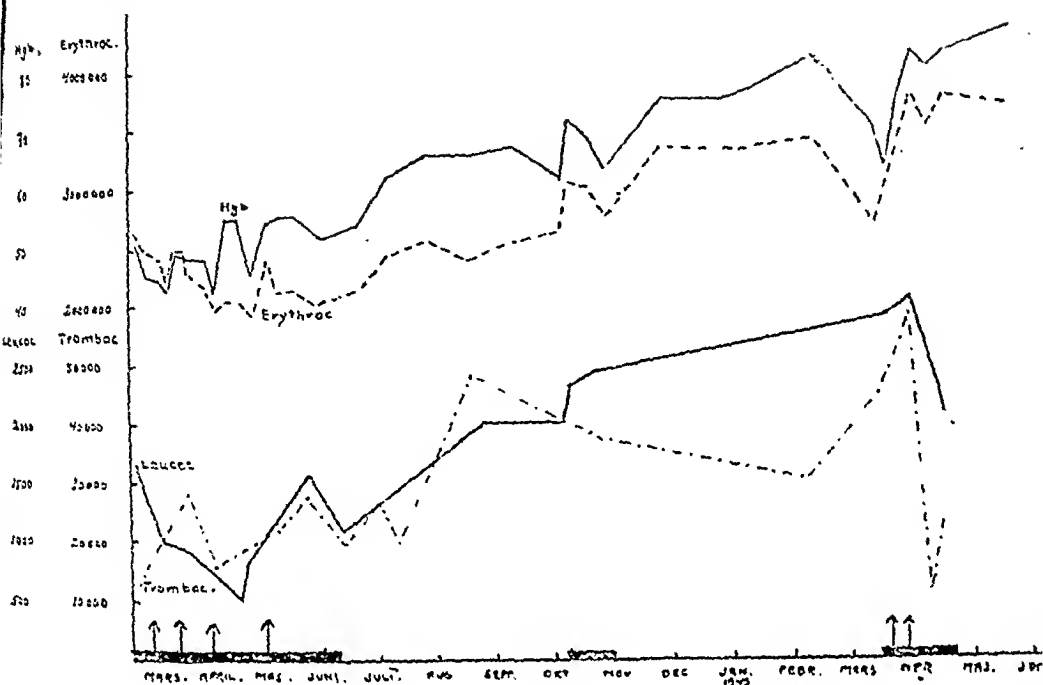


Fig. 7: Case 4. The thick base-line gives the time of treatment in hospital, the arrows show blood transfusions.

She was given *inter alia* repeated blood transfusions, Fe, Campolon. In spite of this the blood values went down. Particular cause for worry when the leukocytes went down to 580/mm³. General condition relatively unchanged. She felt tired and had a great many cutaneous hemorrhages. The bleeding-time dropped in one month to 2 minutes. See fig. 7. After being discharged the patient was treated at the Out-Patients Dept., and also for two short periods in hospital again. Hemoglobin and red corpuscles showed improvement, white corpuscles and thrombocytes were behind-hand. General condition now good, but she still gets a great many cutaneous hemorrhages. She is tired and unable to work.

Case 5.

Anna K. 38 years. No. 483/42.

Previously healthy. For last two months had been tired, sleepy, and had got cutaneous hemorrhages. Treated at the Medical Dept. 28/2—30/5 1942.

From the status: General condition good. Abundant small hematomas on arms and legs, and numerous petechiae. Hb: 50 %, red corpuscles: 2.38 million, white corpuscles: 1,700. Thrombocytes: 6,600.

Diff. count: Gran. 9 %, Plasma cells 1 %, Lymph. 86 %, Monoc. 4 %.

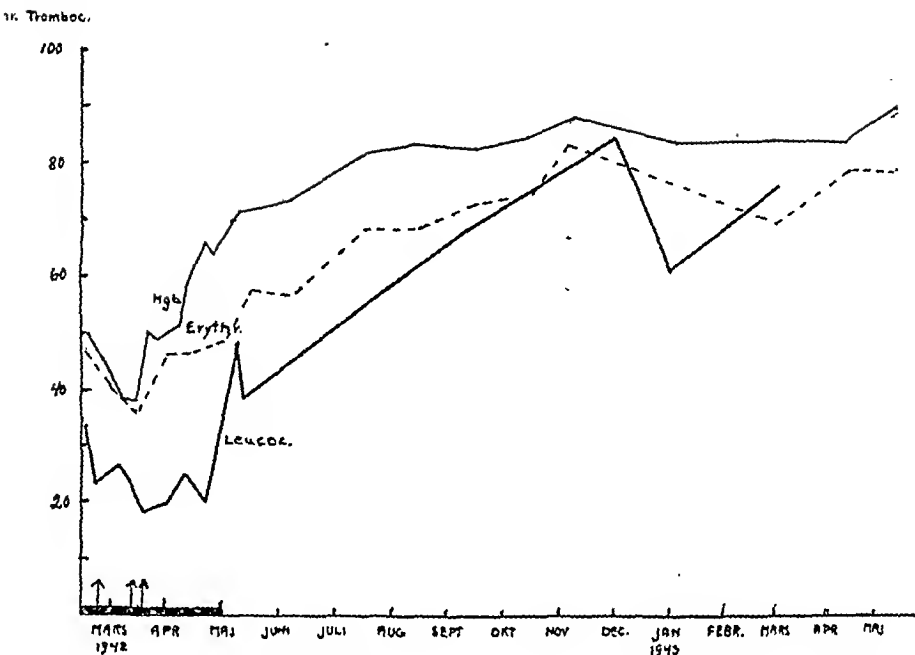


Fig. 8: Case 5. The thick base-line gives the time of treatment in hospital, the arrows show blood transfusions.

Bleeding-time: 11 mins. Coagulation-time 17 mins. Prothrombin determination normal. SR: 97.

During her stay in hospital the patient's general condition was good throughout. Afebrile. The bruises disappeared relatively quickly. The bleeding and coagulation-times returned to normal in 2 months. The differential count showed a shift in a lymphocytary direction, so that on discharge she had: Gran. 49 %, Eos. 11 %, Lymph. 30.5 %. Monoc. 9.5 %. This eosinophilia is probably a chance occurrence, and has not been found in other patients. The thrombocytes increased again, and on her discharge on 29/5 were 101,000. The sedimentation rate kept at 90—121 mm the whole time, to fall when she had passed her crisis at the end of March. On discharge it was 8 mm. For other examinations see fig. 8. A remarkable fact is that, in spite of the treatments with blood transfusions etc., the hemoglobin and red and white corpuscles dropped considerably during the patient's stay in hospital, to rise again subsequently. After being discharged she improved still more. As usual the thrombocytes were behindhand.

29/9 1942: 160,000; 18/1 1943: 158,000; 1/6: 174,000. See the curve. The patient feels pretty well, but easily gets tired and short of breath. Discharged as well on 1/6 1943, to begin undangerous work.

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Rapidly recurrent gastric hemorrhage.

By

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(Submitted for publication April 18, 1944).

At the beginning of 1943 we made a survey of our results concerning gastric hemorrhage in the Zuider Ziekenhuis at Rotterdam. Although the number of cases was not great, there was one characteristic which this survey brought out very clearly, which decided us to revise our treatment to some extent (Febr. 1943). We detected in fact a special indication for operative treatment. Simultaneously with the results with this change in therapy, we thought it would be of interest to publish our conclusions, notwithstanding the fact that the number of cases is small.

Our treatment at first was as follows:

We started from the point of view that every gastric hemorrhage should be treated internally. When a patient is taken up in a state of shock (either still bleeding or immediatly after the hemorrhage) if the shock is great or the hemoglobin very low, we administer a blood transfusion per intravenous dropping (100 cm³ per hour), which stops the hemorrhage and the shock is usually quickly relieved. The patient is given no food per os before the hemorrhage had ceased for at least 24 hours. Then follows gelatine mixtures per os (1) and a few days later (4—7) we proceed to the ulcer treatment, with increasing quantities of food and strength of mixtures (prac-

RAPIDLY RECURRENT GASTRIC HEMORRHAGE.

tiably in accordance with Leube).¹ If the hemorrhage returned with a patient who had been treated in this way, we began again at the beginning, again blood transfusion, 24 hours fasting, a few days of gelatine mixtures and finally ulcer treatment. In this way we were sometimes obliged to begin at the beginning several times over. If the hemorrhage continued to recur, we proceeded to operative treatment. The number of times that a hemorrhage was repeated before an operation took place, depended upon the general condition. We also operated in cases of slow continuous hemorrhage in which, without an acute large hemorrhage, the hemoglobine content did not rise and the benzidine reaction in the faeces remained positive. But there was always some vagueness about the criterium for operation and the moment at which it should take place. There were no definite rules.

Our survey yielded the following data:
(While reading it will be advisable to follow the schedule of fig. 1).

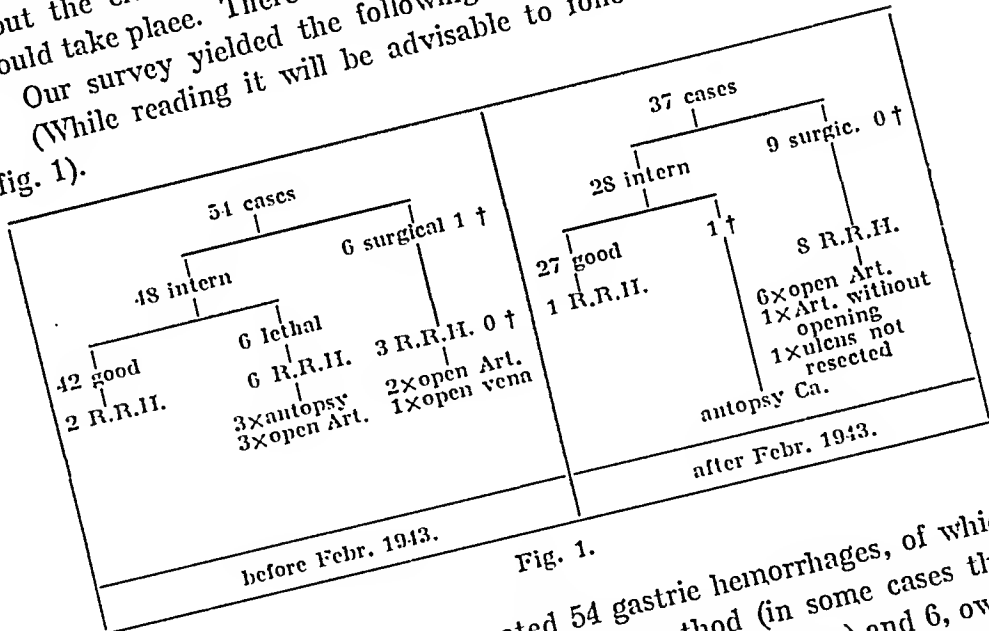


Fig. 1.

Up to Febr. 1943 we treated 54 gastric hemorrhages, of which 48 were treated entirely by internal method (in some cases they were operated upon after the termination of the cure) and 6, owing to the failure of internal treatment, were subjected to operation. Of the 48 internally treated cases 6 ended fatally (12.5 %), the rest

¹ Directly a diet of full value, all food mashed (Meulengracht), was tried to give to 9 patients. 6 of them could not tolerate on account of heavy pains, that started after eating this kind of food. Therefore, the diet of Meulengracht has leaved in this clinic.

recovered without difficulty. We then traced out how these 6 patients had died and what their clinical symptoms had been and observed *that all six cases showed a similarity as regards their clinical symptoms*. In all cases, namely, there was *a rapid recurrence of the hemorrhages*, one of which finally proved fatal. The clinic of these 6 lethal cases follows:

Patient 1. (18/39). A woman, of 51 years of age, who for 30 years had suffered from gastric trouble, had a hematemesis this morning at home. There is no hemorrhage when she is admitted. After 24 hour fasting, proceed in gelatine cure, she has another hemorrhage within 48 hours of admission from which she recovers spontaneously. After another 48 hours a sudden collapse, followed by death before blood transfusion could be given.

Autopsy: Ulcer on the curvatura minor with eroded Art. gastr. sin.

Pat. 2. (1218/40). A man of 49 years of age is admitted on account of gastric trouble. The day after admission suddenly in state of shock, from which he spontaneously revives. The following day again collapse and death within $\frac{1}{2}$ hour.

Autopsy: Ulcus duodeni eroded A. gastr. dext.

Pat. 3. (1229/40). A man of 42 years of age, suffering for many years from gastric trouble, two days before admission had a hematemesis. Immediately after admission he receives gelatine mixtures per os. The following morning patient goes into collapse. Blood transfusion gives so much improvement, that in the evening the patient is in an excellent condition. At night a sudden deep collapse, followed in $\frac{1}{2}$ hour by death.

Autopsy: Ulcus duodeni, eroded A. gastric dext. and two perforations in the pancreas.

Patient 4. (1118/41) A man of 25 years of age on his way to the Out Patients on account of gastric trouble, becomes giddy, vomits blood and collapses. Has revived when he is admitted. He receives an transfusion at once. After 24 hours fasting a beginning is made with gelatine mixtures. Shortly after a collapse from hemorrhage, from which after a time he recovers spontaneously and is in good condition. Six hours later the hemorrhage is repeated and death follows within an hour.

Autopsy: Not possible.

Patient 5. (2048/41). A woman of 68 vomitted blood yesterday, taken ordinary food this morning and then again vomitted blood. She had never had any trouble. On admission she is in a good condition. Two days later, during the gelatine cure she becomes restless, has hallucinations, goes into collapse and succumbs.

Autopsy: not possible.

Patient 6 (2046/42). A woman of 66, after a short period of gastric trouble, is admitted with a profus melaena and seems about to succumb.

A great improvement follows upon blood transfusion. Three days later a sudden collapse, revived by bloodtransfusion to a good general condition. Two days later again a large hemorrhage with fatal result within an hour.

Autopsy: not possible.

Thus 6 similar cases, in which death occurred after the hemorrhage had recurred several times within a short period, the *interval always being less than 72 hours*, while in one case the first recurrence was fatal.

The question therefore arises if it is this rapid recurrence which makes the prognosis unfavourable, in other words »whether as soon as the hemorrhage is rapidly repeated» the prognosis should be considered unfavourable. To answer this we need to know if there have been similar cases amongst the 42 successfully treated patients. It appears that there are only two cases of rapidly recurring hemorrhage in these 42 cases. In both of them there was one recurrence, but no more and in both these cases the recurrence took place within 72 hours. It appears therefore that:

1. Of the 8 cases in which the hemorrhage recurred within 72 hours (once or more) 6 ended fatally, this is a mortality of 75 %.

2. That these patients did not succumb to the first recurrence (in only 1 of the 8 cases did this occur) but to a 2nd. or even to a later one.

3. That in a fatal recurrence death follows within an hour.

It follows that we must not allow these patients a chance of a second recurrence, in other words *operate if possible directly after the first recurrence of the gastric hemorrhage*. It would be difficult to avoid the first recurrence, as we cannot see from the first haemorrhage whether it will be a rapidly recurring one or not. It would force us to operate for every gastric hemorrhage. In our opinion, however, we should try to ascertain which cases of gastric hemorrhage proceed unfavourably with internal treatment and operate only upon these, so as not to subject all patients to the risks of an operation.

Another question arises, namely whether we may keep to the term of 72 hours. As a matter of fact it seems as if this is permissible, considering that in 7 of the cases out of our material in which the hemorrhage was repeated at longer intervals (4—10

days) none ended fatally. Thus it seems as if the special hemorrhage, which is repeated within 72 hours, is a reason for a bad prognosis.¹ In the following we shall indicate this kind of hemorrhage as R.R.H. (rapidly recurring hemorrhage).

Thus, theoretically, there should be an operation after the first recurrence within 72 hours, as the internal treatment in such cases gives such a bad prognosis.

But do we know anything about the prognosis with operative treatment in such cases? In other words, amongst the 6 surgically treated cases (of 54) were there cases of R.R.H.? It appears that there were three, with 1, 1 and 4 recurrences respectively, which were operated upon. The following patient will serve as an example.

Pat. (No. 2097/42). A man of 60, suffering from gastric trouble for 30 years, examined by us in the ward for his complaints. He gets a *melena* there with shock symptoms and recovers after blood transfusion. The following day the hemorrhage is repeated and then again 4 times during the following days. It was then decided to operate, which took place immediately after a hemorrhage, while still in a state of slight shock. The patient stood the operation well and the post-operative course was normal. (resection, Billroth II, was made).

Both the other cases were similar.

The 3 cases of R.R.H., which were operated upon all developed favourably. Therefore in February 1943 we decided to proceed to surgical treatment according to the following indication:

If anyone, of whatever age, has a recurrence of gastric hemorrhage within 72 hours, an operation must take place at once, as soon as the shock has somewhat abated. On no account wait any longer, not even an hour. We shall return in this directly (case No. 1858/43).

Since then (after Febr. '43) we have treated 37 gastric hemorrhages, the results of which follow (see also fig. 1). Of these 37, 8 showed R.R.H. If the recurrence within 72 hours had taken place at home and the patient was brought into hospital in a fair condition without hemorrhage we operated immediately. Even if the patient in such a case is in an excellent general condition, the operation may not be omitted (see case no. 1858/43 p. 382). If the first recurrence took place in the hospital, the patient was immediately operated upon as soon as the shock had been overcome, occasionally even when still in a state of slight shock. During

¹ See also fig. 2.

the operation a dropping transfusion was given. These 8 cases of R.R.H. were in this way almost all operated upon before the 2nd. repetition came (in one case after the 2nd. repetition), and all recovered.

Of the remaining 29 cases there was one who had had the second hemorrhage more than three days before being taken in and where therefore the operation was postponed and proved in fact to be unnecessary. This case, therefore, comes on the list of success for internal therapy.

One patient with a gastric carcinoma succumbed in the first hemorrhage, under internal treatment. All recurrent hemorrhages with longer intervals than 72 hours survived under internal treatment (5 cases).

If we combine these figures, from before and after Febr. 1943 (see also fig. 2) it appears that of the 20 R.R.H. cases:

9 internal treatment with 6 lethal (66.6 %).

11 surgical treatment with 0 lethal¹.

20 R.R.H.	{	9 intern treatment	6 lethal	
		11 surgical	0	
12 S.R.H.	{	11 intern	0	
		1 surgical	0	
10 S.C.H.	{	8 intern	1	(Ca)
		2 surgical	1	(peritonitis 4 days after operation)
49 S.H.	{	48 intern	0	
		1 surgical	0	
R.R.H.		recurring at intervals of less than 72 hours		
S.R.H.		recurring at intervals greater than 72 hours		
S.C.H.		patients continuous slow hemorrhage		
S.H.		first hemorrhage which stops and is not repeated.		

Fig. 2.

Add to this the fact, that the 6 lethal cases are our only lethal cases with gastric hemorrhage (with the exception of the above mentioned Ca. hemorrhage). In our opinion these are figures which, inspite of these limited number, are very significant. In the schedule of fig. 2 we see again that the lethal cases of our material lie especially in the group of the R.R.H. with internal treatment.

¹ In all cases where was operated upon, a resectio ventriculi (Billroth, I or II) was made, up to the present.

We have naturally asked ourselves whether there is an anatomical substratum in this kind of R.R.H. If we examine the pathological anatomy of the stomach revealed by autopsy or resection, we arrive at the following remarkable results.

At autopsy (3 cases) an eroded large artery was always found (art. gastr. dext. or sin). In the 11 resection stomachs an eroded large artery was found 8 times, once a large artery that ran through the base of the ulcer, but where no distinct opening was to be found, once an eroded large vein and once the base of the ulcer was not examined microscopically as it was grown into the pancreas in such a way, that it could not be resected.

Of the 13 times that an ulcer of a R.R.H. was microscopically examined, therefore, an eroded artery was in 11 cases the cause of hemorrhage, while in one case the artery was exposed but the opening could not be found. In the last case no other bloodvessel could be indicated as the cause of hemorrhage.

It is therefore highly probable that when we have a R.R.H. to deal with, there is an erosion of a large artery. This does *not* mean, that we operate «on account» of arterial hemorrhage, we do not know if in a single hemorrhage which has given no cause for operation or has been obducted, an artery might also have caused the hemorrhage, although this is not probable. *We continue to operate, as our experience shows that with the R.R.H. irrespective of age, internal treatment causes a bad prognosis*, while at the same time we would remark that in 85 % the erosion of a large artery is found.

In defining the indications for operation it should be remarked, (p. 380) that we should operate «directly» after the first recurrence and must not wait even an hour, however good the general condition of the patient may be. The following patient will serve as an example to support our conclusions:

Pat. (No. 1858/43). A man of 36, who has had gastric trouble for 7 years, gets a melena with shock three days before being admitted, followed by spontaneous recovery. One day before admittance a hematemesis with giddiness. At admission in a good general condition, no shock symptoms. Patient is quite warm, pulse 96 min., a tension of 110/80 and hemoglobinecontent of 43 %.

The patient has therefore a R.R.H. and in our opinion must be operated upon at once. Considering the good general condition, we thought we might wait a little (3 hours). Immediately before the operation an inter-venous dropping transfusion will be applied with physiologic salt. One

hour before the appointed time for the operation the patient suddenly vomits a large quantity of blood, falls into violent shock. A transfusion is immediately applied and after two hours the shock is pretty well overcome, so that we proceed to operate. It appeared that there was an ulcer ventriculi with erosion of Art. gastric sin.

If the patient had been operated upon immediately, we should have saved him from the danger of the second recurrence, a danger which we now luckily escaped, for if death follows it comes an hour after the beginning of the hemorrhage (see our lethal cases). By this example we wish to show that the recurrences may come very quickly one after another, a fact, which we must take into consideration, and therefore must not delay the operation. Moreover it shows, that the good general condition should not deter us from immediate action. In our opinion these cases of R.R.H., like gastric perforations, belong to the department of acute surgery.

We will by no means maintain, that if we follow these indication, we shall always operate upon a bleeding ulcer, although this will frequently be the case. Cases of spleen or liver and spleen swelling fall outside these considerations. The tables of Bulmer show (2) that the origin of a hematemesis in 89 % is an ulcer and in 5 % a carcinoma. It is quite possible that a Ca. may be found sometimes while operating. But the fact of the possibility of a Ca. is by no means a contra-indication for operating, if we realise the high mortality from R.R.H. Even with men of advanced age, although their complaints may be only recent, the R.R.H. should be an indication of immediate operation. We operated upon 4 patients more than 60 years of age, all ulcers, upon this indication. In this connection Stolte says «as long as the diagnosis is not established we should be just as active as with an ulcer hemorrhage, even with persons of advanced age with a «short» anamnesis» (3). If the diagnosis of Ca. is certain, Stolte considers it an additional reason for operation.

That this method of treatment has introduced a new indication is not the case, it is only that in our material the indication comes out so strongly that we consider it worth while to communicate our experience.

It is no new theory that the recurrence of a gastric hemorrhage should be taken as a reason for operation. Hurst (1929) (4) considers that internal therapy, beginning with 24 hours fasting is

preferable, except when the hemorrhage recurs before the patient has received anything per os, in which case operation is necessary. Hymans van den Berg (1930) (5) and Savy (1940) (6) take up the same point of view. Eusterman and Balfour (1935) (7) operate only on a recurrence of hemorrhage, mention no interval. In 1933 Papin and Wilmoth (8) come to the conclusion that operation must take place when:

1. the ulcer angiotérébrant (with erosion of artery).

- 2 recurrence of hemorrhage.

The ulcer angiotérébrant according to him is probable, when «with a long ulcer-anamnesis, the hemorrhage, slight at first, recurs rapidly».

It is remarkable that in the 11 eroded arteries of our material, we always experienced abundant large hemorrhages and not a single small one.

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From Ullevål Hospital, (Oslo) Dept. VIII. Chief Physician: Carl Müller,
M. D.

The Electrocardiogram in Aortic Insufficiency, with special regard to the development of the left bundle branch block electrocardiogram.

By

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(Submitted for publication May 15, 1944).

In the course of the last ten or twelve years there has crystallized out of the large and somewhat obscure group of electrocardiograms going under the name of myopathia cordis etc. a type, or rather several types of electrocardiograms, which may be summarized under the designation electrocardiograms of left ventricular hypertrophy.

When Thingstad and I in 1938 (5) were investigating the cardiovascular changes in essential hypertension these electrocardiograms aroused our interest in special degree. In the first place we noted, in concordance with other investigators, the great frequency of such types of electrocardiogram in hypertension. Secondly, we believed to have proved that the enlargement of the heart, or rather of the left ventricle, was the decisive factor in producing these types, as there was a distinct correlation between the size of the heart and the electrocardiographic type. This view was decidedly in conflict with the opinion that such electrocardiograms were due to coronary sclerosis and anoxemic changes. Thirdly, we thought to have shown that the left bundle branch block electrocardiogram (new terminology) must be regarded as a further stage

of development of the electrocardiogram of left ventricular hypertrophy, being the electrical manifestation of the highest degrees of left ventricle enlargement. According to this view the principal, but not the sole cause of the left bundle branch block electrocardiogram was to be found in an extreme enlargement of the left ventricle, and not in local lesions of the branches of the His-Tawara system.

In subsequent investigations I have assembled clinical data (7) in support of this view, and have shown by experiments (6) that it is possible by acute dilatation of one half of the heart to produce a retarded conveyance of impulses to a ventricle, attended by the production of bundle branch block electrocardiograms.

Our material comprised patients with hypertension. It was then natural to investigate the form of the electrocardiograms in other cardiac diseases, the chief hemodynamic effect of which was extra work for the left ventricle and consequent hypertrophy thereof. In order to answer this question the present material of patients with aortic insufficiency has been collected from Ullevål Hospital, Dept. VIII.

In the first instance, it is of interest to ascertain, by the same investigator and with the same methods of investigation, how frequently these forms of electrocardiogram occur in such lesions of the left ventricle, and especially how strongly the left bundle branch block electrocardiogram is represented. Detailed analyses of the left axis deviation and of the importance of high voltage are also desirable. As the left bundle branch block electrocardiogram is chiefly characterized by the broad QRS complex, it is necessary to try to show that a lengthening of the QRS interval is also to be seen in the other electrocardiographic forms of hypertrophy. In a mass investigation, however, this is especially difficult to ascertain, as the expected increases must be relatively small in proportion to the normal range of variation of the QRS complex. Meanwhile the purpose might perhaps be better attained by following the development of the electrocardiogram in one and the same patient.

In studying the electrocardiographic types in relation to the teleroentgenogram, a question of special importance for our problems, we have here, as in 1938, employed the heart-thorax index, Groedel's index, although we might certainly have desired actual

determinations of the heart-volume. In favour of the use of the heart-thorax index for this particular investigation it may, however be mentioned, firstly, that it is the enlargement of the left ventricle that is here of especial interest and precisely such enlargement is clearly revealed by this index, secondly that the index is employed for a series of hearts in which only one and the same mechanical defect manifests itself. Moreover, the use of the semi-direct precordial leads was well suited to illustrate the relation between the left ventricle hypertrophy curves observed and the left bundle branch blocks found, as has been done by Wilson, Mortensen (3) and others.

Weber (9) and others believed that coronary changes and consequent anoxemia of the conductive system constituted the main cause of the hypertrophy electrocardiogram. It then seemed natural to investigate the occurrence of angina pectoris in connection with the different forms of electrocardiogram, as well as the frequency of cardiac infarction and, where autopsy had been made, also the condition of the coronary arteries.

Of special interest are, finally, such cases as those in which the electrocardiogram changes during the course of the illness, sometimes from one type to another. Hereby one will find support for the correctness of regarding the mentioned types as different stages of development and will obtain information as to simultaneous changes in the size of the heart and the QRS interval:

The material consists of 84 patients with aortic insufficiency, 56 men and 28 women. The age distribution is shown in *Table 1*.

Table 1.
Age Distribution in 84 Cases of aortic Insufficiency.

Age	11—20	21—30	31—40	41—50	51—60	61—70	71—80	81—90	
Number	1	1	7	14	19	32	8	2	Total 84

23 of them died and of these were 19 autopsied. 54 were undoubted syphilitics, with positive Wassermann reaction, including one with congenital syphilis. 8 were certainly syphilitic, with negative Wassermann but positive Meinicke Klärung II. 6 showed negative seroreaction, but of these 4 patients had positive anamnesis

and autoblood was examined. Of these typhoid vaccine is the only one which has been accepted by the Council on Pharmacy of the American Medical Association as an agent for nonspecific stimulation. All the preparations tested, except Omnadin and autoblood, caused nonspecific capsular swelling substance to be produced. The response to gold and copper, however, was weak in rabbits, and as regards gold, variable or rare in man, as far as could be judged from the observations reported. On treatment over a long period with a constant dose of manganese the content of reactive substance in rabbits gradually decreased. In man, the reactive substance was observed to disappear entirely after a period of manganese treatment, while in response to sulphur the reaction only showed a decrease in strength.

Neither after blood transfusion nor liver preparations (Heptomin Tika) was there any formation of nonspecific capsular swelling substance.

Summary.

Agents which are thought to be effective in nonspecific stimulation therapy were tested for their power to produce Löfström's nonspecific capsular swelling substance, the acute phase protein, human being and rabbits being used as experimental subjects. A description of methods is given.

Type 16 reactive substance was formed in rabbits after injections of manganese salt, gold and copper salt, and sterile milk, but not from the use of Omnadin or autoblood. The most effective materials were salt of manganese, sulphur, and sterile milk. Continuous treatment with a constant dose of manganese and sulphur yielded higher titers at the beginning of the series than at the end.

In man, type 27 reactive substance was formed after injections of manganese, sulphur, and typhoid vaccine, but not after blood transfusion. The effect of gold salt could not be definitely established from the type of patients investigated — chronic polyarthritis. After continuous treatment with a constant dose of a manganese salt the reaction gradually decreased in strength, and in a couple of cases it disappeared completely. It remained

an arborisation block, 12 had pathological electrocardiogram which cannot be placed with certainty among the known types. A couple of them, however, are probably atypical infarction curves.

If we include, as has previously been done, the left b.b. block among the electrocardiograms of left ventricular hypertrophy, we get 48 of these, or 57 per cent of all the electrocardiograms, or

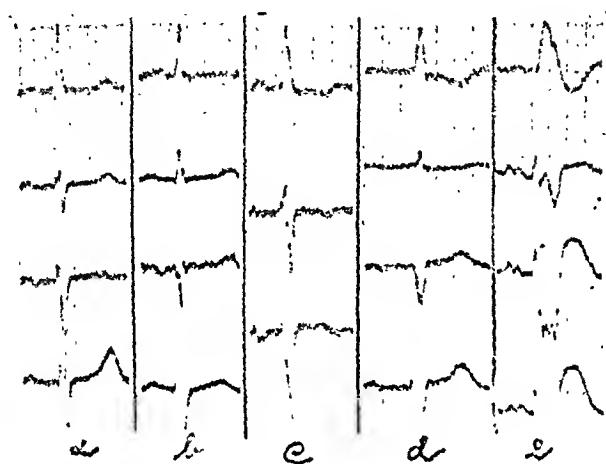


Figure 1.

a. Normal Left axis deviation. b. Type I. c. Type II. d. Type III. e. Type IV. Left b.b. block.

Table 2.

The electrocardiographic Types in Hypertension (R. & T. 1939) and in aortic Insufficiency.

Percentages in Parenthesis.

	Normal electrocardiograms	Left ventricular Hypertrophy				Other pathological forms	
		Type I	Type II	Type III	Type IV. Left B. B. Block		
Hypertension . . .	31	4	14	25	7	19	Total 100
Aortic Insufficiency	16 (19%)	1 (1.2)	10 (12)	31 (37)	6 (7)	20 (24)	Total 84

70 per cent of the pathological forms. Table 2 gives a comparison of the electrocardiographic findings in hypertension and in aortic insufficiency. The left ventricle hypertrophy forms dominate still more greatly in aortic insufficiency than in hypertension, but in

hypertension 50 out of 68 pathological electrocardiograms were left ventricular hypertrophy types, *i.e.* 72 per cent, that is to say the same figure. Of considerable interest is the fact that type IV, the left b.b. block, is equally well represented in both materials.

With respect to the disturbances in rhythm and conduction, 10 patients had permanent and 2 paroxysmal auricular fibrillation, 2 had flutter, 2 nodal rhythm and 2 numerous ventricular extrasystoles. 9 patients had atrioventricular conduction disturbances, which in four of them were considerable, with P—Q measuring 0.24 sec. or more. Three of these latter were rheumatic. The patient with rheumatic fever in the anamnesis, with Bechterew's disease and aortic insufficiency had an atrio-ventricular conduction lasting 0.44 sec.

In the further analysis of the electrocardiograms we shall devote special attention to the normal types and the different forms of left ventricular hypertrophy electrocardiograms, including left b.b. block, and shall try to elucidate the relationship between these various forms.

Left axis deviation. Among the 16 normal cases 8 have no distinctly marked axis, 2 have right axis deviation, 5 left axis deviation and 1 has a variable axis. Whereas left axis deviation was formerly included in the definition of the hypertrophy curves, this principle has here been departed from in 8 cases. In these 8 cases, of types II and III, R_I is no doubt high, but S_{III} (Q_{III}) is not deep. In other words, lead III does not yield the typical picture. It seems justifiable to assign these curves to the electrocardiogram of left ventricular hypertrophy for the following reasons: Firstly, because lead I is entirely characteristic, secondly, because (Fig. 2) the deep S_{III} may wax and wane with the respiration, thirdly, be-

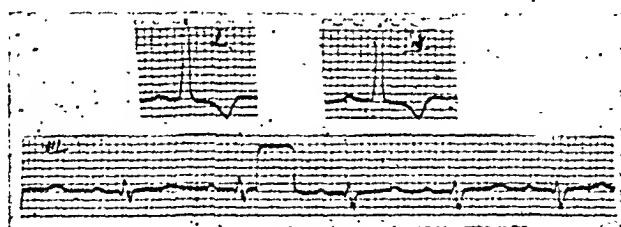


Figure 2.

No. 78. Left ventricular hypertrophy curve without left axis deviation. Respiratory changes in lead III.

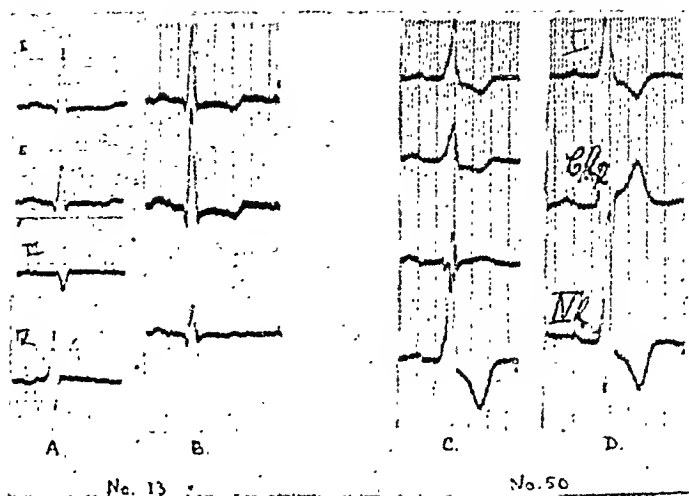


Figure 3.

Left ventricular hypertrophy curves without left axis deviation.

No. 13.

No. 50.

A. 19th Nov. 1936: Left axis deviation.
B. 16th Nov. 1937: High RIII.

C. Ordinary leads.
D. Lead I, CR₂ and IVr.

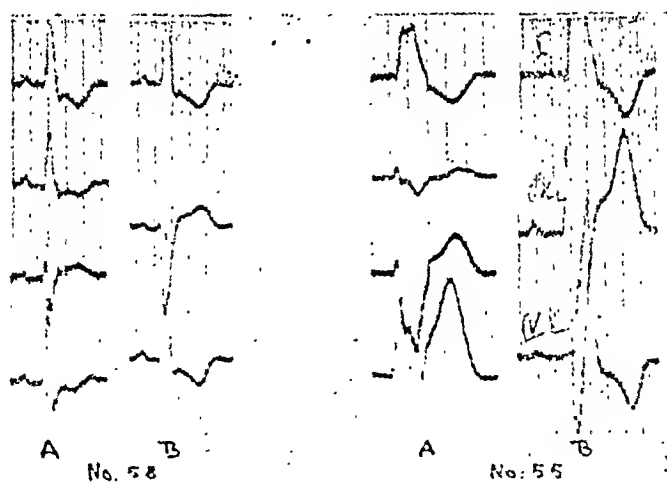


Figure 4.

Precordial leads in left ventricular hypertrophy and in left b.b. block.

No. 58.

No. 55.

A. Left ventricular hypertrophy.
QRS = 0.10.
B. Lead I, CR₂ and IVr.
Interval between intrinsic deflections
0.04 sec.

A. Left b.b. block. QRS = 0.18.
B. Lead I, CR₂ and IVr.
Interval between intrinsic deflections
0.12 sec.

Table 3.

Normal Electrocardiogram and left ventricular Hypertrophy Types. Voltage QRS Interval and cardiothoracic Index. Averages.

		Normal electro- cardio- grams	Left ventricular Hypertrophy			
			Type I	Type II	Type III	Type IV Left B. B. Block
Aortic Insufficiency	Number	16	1	10	31	6
	Height of R _I Average	9	(10)	18.2	16.3	12.8
	QRS Interval in 1/100 sec. Average ..	7.6	(11)	8.3	8.9	15.3
	Cardiothoracic Index, Average	2.04	(1.94)	1.70	1.69	1.57
Hyperten- sion 1939	Number	31	4	14	25	7
	Cardiothoracic Index, Average	1.96	1.80	1.75	1.68	1.61

cause (Fig. 3) the same patient may have typical changes in lead III in one electrocardiogram, while these may fail to appear in the next, fourthly and lastly, because the findings in the precordial leads (Fig. 4) are those typical of left ventricular hypertrophy (see later).

High voltage. In the 16 normal electrocardiograms high voltage, which may be defined as an R_I deflection equal to or exceeding 15 mm, was not observed in any case. The average voltage (see Table 3) is 9 mm (m. v. equals 10 mm). In type II there are found two electrocardiograms with R_I less than 15 mm, eight with 15 mm or more, whereof five are 20 mm or more in height. The average height of R is 18.2 mm. In two electrocardiograms of type III R_I is less than 10 mm in height, in 9 it is between 10 and 15 mm, while 20 have an R_I of 15 mm or more, in 7 of which it is 20 mm or more. The average height of R_I is here 16.3 mm. In type IV, left b.b. block, only two have an R_I of 15 mm or more, while two have only 5 and 6.5 mm respectively, and the average height is 12.8 mm. High voltage, judged by R_I, is thus rather characteristic of the electrocardiogram of left ventricular hypertrophy, although it is not always present and is least conspicuous in the b.b. block curves, doubtless on account of the great widening of the QRS complex.

Table 4.

The Relation of the Heart Size (cardio-thoracic Index) to the Duration of QRS Interval.

Correlation Table.

The Duration of QRS Interval, 1/100 sec.	19—19.9			1
	18—18.9			
	17—17.9		1	
	16—16.9			1
	15—15.9			
	14—14.9			1
	13—13.9			
	12—12.9			1
	11—11.9		1	6
	10—10.9	1	4	5
	9— 9.9	2	1	10
	8— 8.9	1	7	1
	7— 7.9	5	4	
	6— 6.9	2	1	
		2.29—2.00	1.99—1.70	1.69—1.40
Number of Cases		11	19	26
Average QRS Duration		7.6	8.3	10.2

The QRS interval. In the hypertension material investigated in 1939 we found among 43 left ventricular curves (types II and III) 15 with a QRS interval of 0.10—0.11 mm. In the present material the average duration QRS in normal electrocardiograms (Table 3) is 0.076 sec., in type II 0.0825, in type III 0.089 and in type IV 0.153. We shall revert to this point when dealing with the electrocardiographic development in the individual cases. It is known that in small animals the QRS interval is short, in large animals long, which fact is by Wilson regarded as having relation to the thickness of the ventricular wall (my own data: QRS duration in rat 0.015 sec., in dog 0.03, in infant child 0.035, in adult person 0.07. White: in elephant 0.16) — In Table 4 it is sought to find a correlation between the length of the QRS interval and the size of the heart (size of left ventricle). Owing to the smallness of the material investigat-

ed the table cannot be said to prove, although it strongly suggests, that the larger left ventricle has a longer QRS interval.

Relation between size of heart (left ventricle) and type of electrocardiogram. In five cases serviceable teleroentgenograms are lacking. In Table 3 is given the average heart-thorax index for the normal electrocardiogram and for the left ventricular hypertrophy forms, and here are also set forth the findings in the hypertension material. In both materials we find the same tendency towards larger hearts in case of increasing numerical order of left ventricular hypertrophy. The concordance between the two groups of material must be said to be very good. The correlation table (Table 5) shows in detail the same picture. *The semi-direct precordial*

Table 5.

Correlation Table.

The electrocardiographic Types in Relation to the Heart Size.

	Normal	Type I	Type II	Type III	Type IV	
1.30—1.39			1			
1.40—1.49			1	5	1	
1.50—1.59				4	2	
1.60—1.69			3	9	1	
1.70—1.79	1		1	4		
1.80—1.89	2		2	4	1	
1.90—1.99	2	1	1	2		
2.00—2.09	2		1	1		
2.10—2.19	3			1		
2.20—2.29	3					
	13	1	10	30	5	Total 59

leads CR2 and IVR present a characteristic appearance in the curves for left ventricular hypertrophy. In the lead CR2, R is either absent or else is small or relatively small, S is deep, ST is elevated and T high positive. The lead may be said to resemble the third lead. The lead IVR, has a high R, depressed ST and negative T, and it resembles the first lead. If CR2 and IVR are registered simultaneously (Fig. 3 and Fig. 5), the late activation of the left

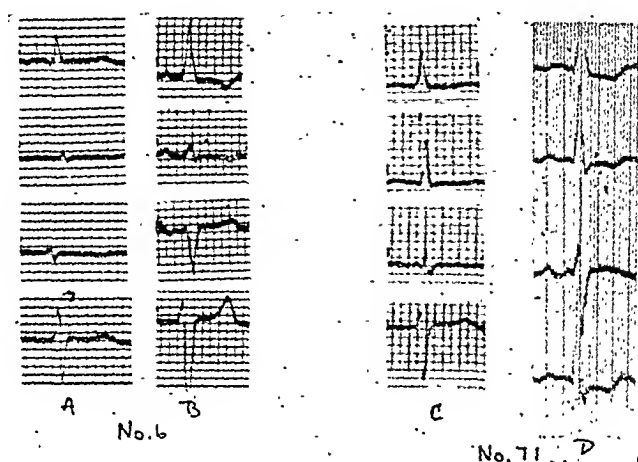


Figure 5.

Development of left ventricular hypertrophy curves from normal electrocardiograms.

No. 6.

- A. May 1937. QRS = 0.07 sec.
Cardio-thoracic index = 1.97.
B. Oct. 1938. QRS = 0.09 sec.
Cardio-thoracic index = 1.46.

No. 71.

- C. Febr. 1941. QRS = 0.08 sec.
Cardio-thoracic = 2.00.
D. Dec. 1942. QRS = 0.11.
Cardio-thoracic index = 1.84.

ventricle, expressed by the retarded intrinsic deflection over the apex, is very finely shown (Lewis, Wilson, Mortensen). These characteristic features were observed in 16 of the 18 cases investigated, while 2 were only slightly atypical. In 14 cases of hypertrophy curves, types II and III, the typical picture was seen, and likewise in 2 cases of left b.b. block (type IV). The M-shaped complexes which Mortensen (3) found in IVF in cases of left b.b. block has not been observed by me either in this or in previous investigations.

It has been sought to estimate *the frequency of coronary diseases* by noting the occurrence of angina pectoris and myocardial infarction. 23 patients, or 27 per cent, had troubles which must be classed as angina pectoris. The distribution of angina pectoris in relation to the electrocardiographic types is shown in Table 6. The same frequency of angina pectoris, namely, a little under one-third, is found, perhaps somewhat surprisingly, in all groups. This distribution speaks against the view that coronary disease forms the basis for the hypertrophy curves. In 6 cases clinical infarctions were present. 5 of these patients had infarction electrocardiograms, while one had a left b.b. block electrocardiogram, which

Table 6.

Frequency of Angina Pectoris in the different electrocardiographic Types.

	Normal Electro- cardio- grams	Type II	Type III	Type IV	Atypical
Patients with Angina Pectoris	5	3	9	1	5
Total Number of Patients	16	10	31	6	15

remained unchanged after the infarct appeared, with precordial friction etc. Two of the diagnoses of myocardial infarction were verified by autopsy. One was in the anterior and one in the posterior wall. Otherwise it is somewhat remarkable that four infarction electrocardiograms were of the posterior wall type, a fact which merely illustrates the difficulty of diagnosing anterior wall infarction electrocardiographically when a left hypertrophy electrocardiogram is present. Infarctions superimposed upon hypertrophy curves sometimes produce difficult electrocardiographic pictures, and among the atypical forms there are probably a couple of such cases. The employment of multiple precordial leads is here undoubtedly of advantage.

In all of the 19 autopsies recorded good passage through the coronary arteries was found, except in one case with infarction of posterior wall, where the right coronary artery was occluded. A moderate degree of fibrosis was noted in five cases. It might be added that 6 patients with left ventricular hypertrophy electrocardiograms, one of type II, 5 of type III, had no other sign of cardiac dysfunction.

An alteration in electrocardiographic types during the course of the illness was observed in 7 patients. In 5 of them the electrocardiogram in the course of from 10—17 months to 6—8 years changed from normal or slightly abnormal form to a left ventricular hypertrophy curve, type III (Figs. 6 and 7). In three of these the heart during the same period became considerably enlarged, while in one patient with pulmonary tuberculosis it showed no certain alteration. In one patient the electrocardiogram changed from type III to type II in the course of a few days (regression of left ven-

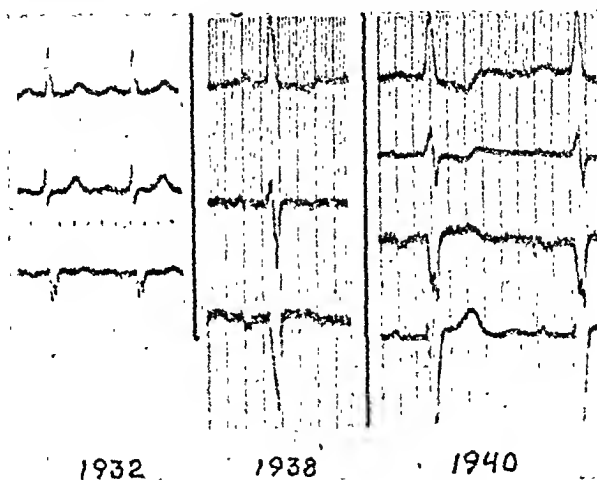


Figure 6.

Development of left ventricular hypertrophy curve from normal electrocardiogram.

No. 56.

1932. Normal electrocardiogram. QRS = 0.08 sec.

1938. Left ventricular hypertrophy. Type II. QRS = 0.09—0.10 sec.

1940. Left ventricular hypertrophy. Type III—IV. QRS = 0.11—0.12 sec.

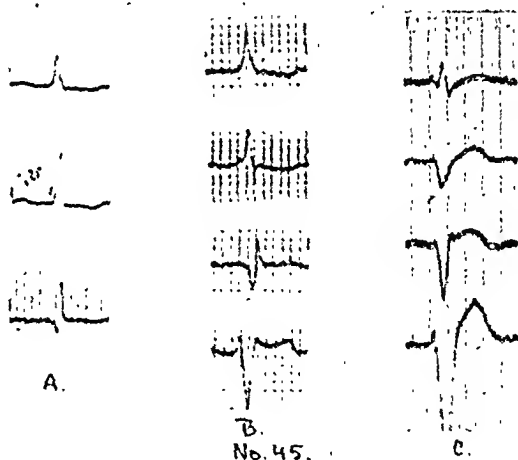


Figure 7.

Development of left b.b. block (type IV) from type II and III.

No. 45.

A. March 1933. QRS = 0.09 sec.

B. Jan. 1936. Auricular fibrillation. QRS = 0.10 sec.

Cardio-thoracic index = 1.55.

C. May 1940. QRS = 0.14 sec.

Autopsy May 1940. Heart weight 1120 g.

Thickness of left ventricular wall 25 mm.

tricular dilatation?). Of special interest is No. 45, where the electrocardiogram changed from type II to type III in three years and in the course of the following four years passed over to type IV, left b.b. block. Noteworthy is also the QRS interval, which in 4 out of 5 patients, with development from normal electrocardiogram to type III, was distinctly and considerably increased in one case by 0.02 sec., in three by 0.03 sec. One patient had only a slight and doubtful increase (0.005). On development of b.b. block in No. 45 the increase was 0.05 sec.

During the assembling of the material 6 cases of rheumatic combined mitral stenosis and aortic insufficiency, three of which were autopsied, were separated out. These electrocardiograms are of interest as a «negative control group». Two of them are left ventricle hypertrophy electrocardiograms, of type II and type III respectively. Two have distinct right hypertrophy curves, two have pronounced right axis deviation, one of these being on the threshold of right ventricle hypertrophy. Thus a supervening mitral stenosis entirely alters the electrocardiographic picture in aortic insufficiency. Among the 84 patients with aortic insufficiency alone no case with right hypertrophy curves was found.

Discussion.

In the investigation of hypertension material made in 1939 (5) 50 out of 69 pathological electrocardiograms, *i.e.*, 72 per cent, were of types characterized by left ventricle hypertrophy, including also left b.b. block. In the present material, where another pathogenetic factor, namely, aortic insufficiency, occasions left ventricle hypertrophy, we find, with the same classification, that 48 out of 68 pathological electrocardiograms, that is to say, likewise 70 per cent, indicate hypertrophy of the left ventricle. Not only do we find the left ventricular hypertrophy curves equally predominant in both materials, but also the left b.b. block, which we have previously regarded as the maximum degree of left hypertrophy, is equally represented in both groups.

By classifying the electrocardiograms expressive of the left ventricular hypertrophy and dilatation (more correctly: left retardation electrocardiograms) into 4 different types it has also here been sought to show that these types represent stages in a process of development and that this development is determined by va-

rying degrees of left ventricle enlargement. The most important point in this reasoning is the finding that the left hypertrophy electrocardiogram of type III is a precursory stage of and passes over to type IV, namely, to the left b.b. block electrocardiogram, and that both are expressive of different degrees of left retardation due to varying enlargement of the left ventricle, occasioned by hypertension or by aortic insufficiency. According to this view the principal, but not the only cause of left b.b. block is the great enlargement of the left ventricle.

Left ventricular hypertrophy curve of type I is represented in the hypertension material by 4 cases, in the present material by 1 case. This type therefore does not admit of any very searching examination and is of no great importance. Type II presents the difficulty that it may be simulated by changes due to digitalis. It is not always easy with certainty to preclude the effects of digitalis, but in a number of cases it has been possible to do so.

Left axis deviation can no longer be deemed requisite for the diagnosis of the left ventricle hypertrophy curves, as the third lead needs not necessarily reveal a deep S. In 8 out of 41 hypertrophy curves (types II and III) the changes have been absent in the third lead, or have been only occasionally found. This is in accordance with Kaplan and Katz's findings (2). It also accords with Robert's demonstration (8) that the first lead is of greatest importance as regards the seat of the b.b. block lesions. While it was originally believed (Lewis) that left axis deviation was *the sole sign* of left hypertrophy, it has thus been reduced first to being only *one* of the signs and now even to being unnecessary for demonstration of the left ventricular hypertrophy electrocardiograms.

As in the hypertension material, it is also here found on examining the relation of the electrocardiographic types to the tele-roentgenograms that the different forms of left ventricular hypertrophy, according to their numerical order, are associated with increasing degrees of roentgenologically recorded cardiac enlargement. We are here assuming that the enlargement applies mainly to the left ventricle, but in some cases this assumption, judging from the roentgenogram, does not hold good, and large hearts are then occasionally found without corresponding changes in the electrocardiogram. That the size of the heart increases with the rise in the typenumber for hypertrophy seems to appear both

from the average figures for the heart-thorax index in each type of electrocardiogram and from the correlation table. Noteworthy is also the great similarity between the heart-thorax indexes for one and the same type in hypertension and in aortic insufficiency respectively.

The precordial leads in the pronounced forms of hypertrophy and in b.b. block have exactly the same appearance. As has previously been shown by other investigators, these leads indicate a retarded activation of the left ventricle, *i.e.*, the same fundamental process is operative in all these forms.

Against the interpretation of the left hypertrophy curve as being the precursor of left b.b. block it has, with good reason, been objected that an increase of QRS must also have been visible in the hypertrophy electrocardiogram, and such increase has not previously been demonstrated. The average figures for the duration of QRS in the different types show, it is true, some increase, but hardly sufficient to permit of drawing any definite conclusions in such a small body of material. As was to be expected, the attempt to find a correlation between the QRS duration and the size of the heart (left ventricle) may indicate, but does not prove, such a relationship. On studying the development of the individual cases, however, there has been found a distinct increase of the QRS interval, on transition from the normal electrocardiogram to the left ventricular hypertrophy curves.

The fact that the frequency of angina pectoris is equally great, whether the electrocardiogram is normal or shows hypertrophy or other pathological changes, speaks against the interpretation of the hypertrophic electrocardiogram as an indication of coronary sclerosis with anoxemia, for instance in the conduction system.

Attention has especially been directed to cases where the development from normal electrocardiograms to hypertrophy curves, or perhaps from one type to another, could be followed. In 5 patients the transition from normal electrocardiogram to hypertrophy electrocardiogram of type III was observed. 3 of the 4 cases where effective roentgen examination was carried out show at the same time a considerable increase in the size of the heart. The widening of the QRS has already been mentioned. In one patient it was found possible to follow the development from hypertrophy of type II to type III and further to type IV, left b.b. block.

Summary.

1. In 84 patients with aortic insufficiency electrocardiograms of the types showing left ventricular hypertrophy predominate among the pathological types to the same degree as was previously found in cases of hypertension, 70 per cent of the pathological electrocardiograms being left ventricular hypertrophy forms, including b.b. block. Left b.b. block occurs with the same frequency (7 per cent) in both of these left ventricular heart diseases.

2. Left axis deviation needs not necessarily be present in left hypertrophy electrocardiograms, seeing that the deep S(Q) in lead 3 may be lacking.

3. The electrocardiograms of left ventricular hypertrophy are divided into four types and it is shown that these types represent stages in one and the same process of development. Corresponding to these electrocardiographic stages are found increasing degrees of enlargement of the heart (left ventricle).

4. That b.b. block in these lesions of the left heart represents a further stage of development of the hypertrophy curves is proved: a) by study of the size of the heart, b) by precordial leads, c) by the observation of an increased QRS interval also in the hypertrophy curves, d) by the direct development of b.b. block in a patient who had previously had the typical electrocardiogram of left ventricular hypertrophy (types II and III).

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Anemia hyperchromica diphyllbothrica.

By

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Introduction.

Since the end of the last century it has been known that the broad tape-worm (*Diphyllbothrium latum*) may occasionally cause a disease which cannot be distinguished from the so called cryptogenetic pernicious anemia. An other similarity in the two diseases has later been discovered, i.e. that treatment with liver- and stomach-preparations, which is essential in cryptogenetic pernicious anemia, is very effective in pernicious tape-worm anemia (*Anaemia perniciosa diphyllbothrica*) as well. The number of persons taken ill with pernicious tape-worm anemia is very small in comparison with the number of tape-worm carriers — they are only a fraction of one per cent. Besides this very much investigated, and if I may say so, generally acknowledged anemia, caused by tape-worm, there are other types of anemia which have been connected with infestation with tape-worm. Hoff and Sauerstein consider that the broad tape-worm very often causes an anemia of hypochromic type. Sehauman, who, on the contrary, has had 3 cases of chlorosis in tape-worm patients considers the occurrence incidental. He based his conception on the fact that the blood-picture improved quickly by treatment with iron, as chlorosis generally does, though the tape-worm was not expelled. Vesa is of the same opinion after a negative result with liver in a case of tape-worm

and hypochromic anemia. Yet none of these authors have tried the effect of anthelmintic treatment alone in the case of hypochromic anemia which would of course be the only means of solving the question of a possible connection between the hypochromic anemia and the tape-worm. Saltzman has in one case of hypochromic anemia and tape-worm seen the reticuloocyte count sink after expulsion of the worm, while large doses of iron showed a clear increase of the count. In none of the ten cases of tape-worm and hypochromic anemia that I have had the occasion to attend have I been able to find an improvement in the blood-picture after an anthelmintic treatment. It does not, therefore, seem to me probable that the broad tape-worm could cause an anemia of hypochromic type. The case is different, however, as regards the light hyperchromic or sometimes almost normochromic anemia which is often found in persons infested with broad tape-worm. This kind of anemia (*Anemia hyperchromica diphyllbothrica*) improves after a vermifuge without any other treatment. I shall give a few examples to illustrate this type of anemia. There is a reason for me to do so, not because the changes in the blood in this disease can compete with the changes in the blood in pernicious tape-worm anemia, but on the account that medical and haematological books do not include a proper description of the light hyperchromic anemia in tape-worm carriers.

G. Becker is the first one to have stated the presence of a light anemia, characterized by a somewhat increased color index, in persons infested with broad tape-worm. He found such changes in the blood in nearly all tape-worm patients that he examined. As they occurred so often Becker considered that they were not to be taken as primary stages of pernicious tape-worm anemia as Ragoza had alleged some time before. Some authors (Hoff and Sauerstein, Odin) investigating the matter at a later date did not find any changes whatever in the blood in most of the carriers. In an investigation, completed in 1939, I was on the other hand able to state the presence of a light hyperchromic anemia in 14.8 per cent of my material of persons infested with broad tape-worm. As this anemia was cured by anthelmintic treatment we must consider the cause of it to be tape-worm infestation. The greater part of my patients did not, however, show any signs of anemia. A light hyperchromic anemia occurs, according to my investigation,

more frequently in tape-worm patients than does pernicious tape-worm anemia and yet it is not so common as in Becker's and Ragoza's material.

Material and Results.

My material comprises 24 cases, 15 women and 9 men, all adults. The corrected haemoglobin value in women varied from 72 to 96 per cent, the mean value was 83 per cent. The red cell count varied between 3,430,000 and 4,376,000 with a mean value of 3,949,000. The color index varied between 1.01 and 1.10 with a mean value of 1.05. In the men the haemoglobin value varied from 68 to 100 per cent, the red cell count from 3,110,000 to 4,600,000, the mean values were 87 per cent resp. 4,130,000; color index 1.00—1.12 with a mean value of 1.08. The anemia is, as seen, very moderate throughout. It may perhaps seem surprising that I have included a case in my material in which the corrected haemoglobin value was 100 per cent, but, in the case in question, the red cell count was 4,470,000 which must be considered too low in a man. Because of the high haemoglobin value the color index was the highest in the whole material, i.e. 1.12. The mean diameter of the red blood cells has been determined in 10 cases and found to be normal. In 14 cases, in which the number of white blood cells were determined, a slight decrease in number was noticed, a case that may be found in tape-worm carriers, too, though no signs of anemia are present.

I have used Ewald's test meal in all cases but one, because, as is known, a deviation from the normal gastric acidity is observed in general in anemia and especially in pernicious anemia. We know, for instance, that the total lack of hydrochloric acid in cryptogenetic anemia is always found and that achlorhydria appears in more than 80 per cent in advanced cases of pernicious tape-worm anemia. In 17 cases gastric acidity was fairly normal. The occurrence of achlorhydria does not appear to me to be too frequent nor does it diverge from what is noticed in non-anemic tape-worm carriers. In the 5 patients with achlorhydria no lower blood values in any form were found than in those that showed normal gastric functions. In tape-worm carriers with light hyperchromic anemia there were no divergencies from the normal in secretory functions, which, however, often is the case in patients with pernicious tape-worm

anemia even after an improvement of the disease as there is still achlorhydria in 50 per cent of the cases. Perhaps a certain support is given herein to the idea — expressed by Becker — that the light hyperchromic anemia in tape-worm carriers should not be considered a primary stage of pernicious tape-worm anemia.

As already mentioned, light hyperchromic tape-worm anemia as well as pernicious tape-worm anemia may be improved by anthelmintic treatment. In the latter case liver treatment is generally very effective, as known, though the worm is not expelled. It seems, however, as if the effect of liver treatment — as Saltzman has pointed out — is somewhat less in pernicious tape-worm anemia than in cryptogenetic pernicious anemia. There are some cases in which the blood values have not quite reached the normal by liver treatment, before the worm has been expelled (Becker, Saltzman). The blood is improved to a certain extent in these cases but the improvement does not continue until the patient has undergone a successful anthelmintic treatment. — How does the light hyperchromic anemia react to liver treatment? We know nothing about it with certainty. I have therefore found it justified to investigate the matter. By using an injectable liver preparation I have hoped to bring out the effect of a pure anti-pernicious liver factor on light hyperchromic anemia in tape-worm carriers.

12 of my 24 patients with light hyperchromic anemia were subjected to a vermifuge which gave a very good result. The blood picture was normal in some weeks though no other treatment was given. In the other 12 cases I tried the effect of an injectable liver preparation (Heptomin Medica) in doses of 3×2.0 . These doses have proved to be sufficient to bring about a complete improvement of the blood picture in the case of typical pernicious anemia. In one of the 12 cases all traces of anemia disappeared in one month. The haemoglobin value increased from 80 per cent to 100 per cent, the red blood cell count from 4,200,000 to 4,960,000. The color index decreased at the same time from 1.07 to 1.01. In 5 cases there was a distinct, yet not complete improvement of the blood picture after liver injections. In the remaining 6 cases it looked as if the Heptomin had not effected the anemia favourably. In 4 of these 6 cases the blood picture was, however, noticeably improved, in one case somewhat less, after a vermifuge had been administered

to them all. The sixth patient did not appear for examination after the vermifuge. — In 4 cases the number of reticulocytes were counted after the Heptomin treatment. An increase was not noticed in any of the cases, not even in the case that improved noticeably by Heptomin treatment. Such a result was expected as the anemia was very slight in all these cases.

Discussion.

An injection of liver preparation thus showed a good result in only one of the 12 cases of light hyperchromic anemia in persons infested with broad tape-worm. In 5 cases the effect was moderate; a vermifuge administered later was, however, effective in these cases. In the remaining 6 cases the Heptomin did not seem to have any effect. The decidedly slight effect of Heptomin on the light hyperchromic anemia in tape-worm carriers appears to me to be important. If this kind of anemia were a primary stage of the pernicious tape-worm anemia an injectable liver preparation ought to be at least as effective as it is in pernicious tape-worm anemia, which is a much more serious disease of the blood. Perhaps this observation may be interpreted as a support to the conception that the two kinds of anemia in tape-worm carriers do not differ in quantity only but also in quality. The few cases of pernicious tape-worm anemia which do not improve by liver treatment alone, without expelling the worm, may be of a kind in which a specially strong component of light hyperchromic anemia is evident. In such a case the lesser effect of liver treatment on pernicious tape-worm anemia than on cryptogenetic pernicious anemia, noticed by Saltzman, may find a plausible explanation. In 1929 Saltzman put forth a supposition in this question as follows: »the liver is adapted to the endogene factor, or, let us say, to a supposed organic insufficiency independent of any outside factors which may have released it; but that it does not influence in the same degree or directly such exogene factors as, for instance, the one represented by *Bothriocephalus*.» Saltzman's and my suppositions do not seem to me to be inconceivable, on the contrary, they seem to me to be quite conceivable. My supposition is a trial to determine the action of the tape-worm more exactly. I should like to make a distinct difference between the light hyperchromic anemia, caused

by a direct poisonous effect of the tape-worm on the blood and the blood forming organs and the genuine pernicious tape-worm anemia. The effect of liver treatment on light hyperchromic anemia is practically as ineffective as on the experimental hyperchromic anemia obtained in animals by certain blood poisons and tape-worm components. The symptoms — dizziness, numbness, burning of the tongue and eosinophilia — often occurring in tape-worm carriers, indicate that components of the tape-worm are absorbed into the blood stream in a great number of cases. This explains why the cases of light hyperchromic anemia are rather numerous. Absorption of tape-worm poison alone will not cause pernicious tape-worm anemia. Other factors must collaborate to produce the disease.

Summary.

The author's material comprises 24 cases of light hyperchromic anemia in persons infested with broad tape-worm. In all these cases the anemia was very moderate, the gastric acidity normal and no connection between the secretion of hydrochloric acid and the anemia was noticed. In 12 of the cases a vermifuge was administered and the effect on the blood picture was good. In the remaining 12 cases the effect of an injectable liver preparation was tried without removal of the worm. The result was good in one case only. A favourable effect was noticed in 5 cases; an anthelmintic given later improved the blood picture still more. In 6 cases the liver preparation seemed to have no effect, while the expulsion of the parasite was effective. The poor effect of liver on the light hyperchromic tape-worm anemia, the normal gastric acidity and the fact that this type of anemia is much more common than the pernicious tape-worm anemia are facts which, according to the author, suggest that both these types of tape-worm anemia are not different stages of the same blood disease. The light hyperchromic tape-worm anemia is perhaps caused by resorption of tape-worm poisons and may be compared with the experimental poison anemias in animals. The pernicious tape-worm anemia will not arise out of this cause alone, other factors must evidently collaborate to produce the disease.

Cases.

Cases 1—12 are contained in the author's treatise »Über Sternalmark und Blut bei Wurmträgern», in which they are cases 63, 66, 71, 73, 74, 77, 83, 86, 92, 98, 99 and 104.

Case 13. Farmer, 40 years. 20. 10. 43. Hb 77/89. E 4,060. I 1.10. HCl 0. Ta 10. Heptomin 3×2.0 . 28. 10. 43. Hb 81/94. E 4,400. I 1.07. 4. 11. 43. Hb 73 85 E. 3,660. I 1.16. Vermifuge 25. 11. 43 Hb 81/94 E 4,250. I. 1. 11. 5. 3. 44 Hb 83/96. E 4,680. I 1.02.

Case 14. Soldier, 23 years. 16. 10. 43. Hb 80/93. E 4,320. I 1.07. Heptomin, 23. 10. 43. Hb 81/94. E 4,600. I 1.02. 30. 10. 43. Hb 84/97. E 4,590. I 1.06. Vermifuge, 6. 11. 43. Hb 80/93. E 4,560. I 1.02. 12. 11. 43. Hb 83/96. E 4,680. I 1.02.

Case 15. Clark, 43 years. 18. 1. 44. Hb 78/90. E 4,490. I 1.00. HCl 0. Ta 18. Heptomin. 26. 1. 44. Hb 81/94. E 4,690. I 1.00. 2. 2. 44. Hb 82/95. E 4,670. I 1.02. 9. 2. 44. 76/88. E 4,090. I 1.07. 16. 2. 44. Hb 72/84. E 4,005. I 1.04. Vermifuge, 24. 2. 44. Hb 75/87. E 4,190. I 1.04. 2. 3. 44. Hb 78/90. E 4,420. I 1.02. 8. 3. 44. Hb 81/94. E 4,540. I 1.03.

Case 16. Farm-labourer, 30 years. 8. 10. 43. Hb 59/68. E 3,110. I 1.09. HCl. 20 Ta 60. Heptomin. 16. 10. 43. Hb 59/68. E 2,960. I 1.15. 27. 10. 43 Hb 66/77. E 3,350. I 1.15. 8. 11. 42. Hb 77/89. E 4,440. I 1.00. 22. 11. 43. 78/90. E 4,250. I 1.06. 2. 12. 43. Hb 68/79. E 3,870. I 1.02. Vermifuge. 14. 12. 43. Hb 84/97. E 4,620. I 1.05. 21. 12. 43. Hb 85/99. E 4,670. I 1.05. 28. 12. 43. Hb 85/99. E 4,770. I 1.04.

Case 17. Soldier, 22 years. 15. 10. 43. Hb 86/100. E 4,470. I 1.12. HCl 20 Ta 45. Heptomin. 2. 10. 43. Hb 86/100. E 4,500. I 1.11. Vermifuge. 26. 10. 43. Hb 85/99. E 4,870. I 1.02. 18. 11. 43. Hb 86/100. E 5,000. I 1.00.

Case 18. Soldier, 22 years. 20. 11. 43. Hb 70/80. E 4,200. I 1.07. HCl 5 Ta 25. Heptomin. 29. 11. 43. Hb 84/97. E 4,500. I 1.08. 7. 12. 43. Hb 85/99. E 4,680. I 1.05. 14. 12. 43. Hb 85/99. E 4,800. I 1.03. 21. 12. 43. Hb 86/100. E 4,960. I 1.01.

Case 19. Soldier, 23 years. 9. 10. 43. Hb 76/88. E 3,660. I 1.20. HCl 29. Ta 48. Heptomin. 18. 10. 43. Hb 80/83. E 3,820. I 1.23. 25. 10. 43. Hb 80/93. E 3,800. I 1.22. Vermifuge. 1. 11. 43. Hb 81/94. E 3,980. I 1.18. 8. 11. 43. Hb 84/97. E 4,170. I 1.16. 15. 11. 43. Hb 85/99. E 4,450. I 1.11.

Case 20. Farmer, 38 years. 20. 10. 43. Hb 73/85. E 3,780. I 1.12. HCl 10 Ta 40. Heptomin. 17. 11. 43. Hb 67/78. E 3,110. I 1.25.

Case 21. Labourer, 39 years. 18. 12. 43. Hb 83/90. E 4,600. I 1.04. HCl 16 Ta 36. Heptomin. 27. 12. 43. Hb 84/97. E 4,640. I 1.04. 3. 1. 44. Hb 86/100. E 4,800. I 1.01. 10. 1. 44. Hb 84/97. E 4,790. I 1.01.

Case 22. Chambermaid, 23 years. 2. 2. 44. Hb 62/72. E 3,430. I 1.05. HCl 18 Ta 44. Heptomin. 9. 2. 44. Hb 70/81. E 4,010. I 1.01. 16. 2. 44. Hb 71/82. E 3,920. I 1.04. 22. 2. 44. Hb 73/85. E 4,020. I 1.05. Vermifuge. 29. 2. 44. Hb 75/87. E 4,200. I 1.03. 8. 3. 44. Hb 77/89. E 4,280. I 1.04.

Case 23. Farmer's wife, 48 years. 22. 1. 44. Hb 70/81. E 3,820. I 1.06. HCl 0 Ta 20. Heptomin. 2. 2. 44. Hb 69/80. E 3,830. I 1.04. 9. 2. 44. Hb 69/80. E 3,910. I 1.02. 16. 2. 44. Hb 63/73. E 3,530. I 1.03. Vermifuge. 23. 2. 44. Hb 71/82. E 3,910. I 1.05. 2. 3. 44. Hb 73/85. E 4,030. I 1.05 8. 3. 44. Hb 77/88. E 4,320. I 1.02.

Case 24. Farmer's wife, 57 years. 28. 1. 44. Hb 67/78. E 3,860. I 1.01. HCl 16. Ta 26. Heptomin. 4. 2. 44. Hb 71/82. E 4,030. I 1.02. 15. 2. 44. Hb 75/87. E 4,300. I 1.01. 23. 2. 44. Hb 75/87. E 4,290. I 1.01. Vermifuge. 29. 2. 44. 77/89. E 4,390. I 1.01.

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On the occurrence of pernicious tape-worm anemia in *Diphyllbothrium* carriers.

By

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Introduction.

Two accounts of the occurrence of pernicious tape-worm anemia in persons infested with broad tape-worm (*Diphyllbothrium latum*) are found in literature. The one, by R. Ehrström, is often referred to in medical literature, the other one does not seem to have become known to any extent. It is included in an essay by T. Seppä. According to Ehrström's calculations, which are based upon approximations by physicians in the provinces, on the tape-worm frequency in various parts of the country and on the presumption that not more than 100 cases of tape-worm anemia occur annually in Finland, the broad tape-worm will cause pernicious tape-worm anemia only in one case of 5,000 to 10,000. Seppä again found one case of tape-worm anemia in 659 persons infested with broad tape-worm. His results were obtained by investigating the occurrence of tape-worm and tape-worm anemia in conscripts admitted into the military hospital at Viborg. O. Schauman and G. Becker, too, have dealt with this question but only en passant. Clinical material gave Schauman the result 1: 100 and Becker obtained the result 1: 168 from material in his private practice. Both these authors consider their material unsuitable and their results too high.

Ehrström's and Seppä's results differ greatly, as seen. Some objections may, however, be raised against Ehrström's calculations. His figure for tape-worm cases are based upon the estimations of provincial doctors and must naturally be somewhat inexact when figures for the whole country are worked out of these figures. We must furthermore take into consideration that the figures 1: 5,000 to 1: 10,000 are not based upon any statistics on the frequency of tape-worm anemia in the whole country and must consequently be very unreliable.

Seppä's results are based upon examinations of patients in an internal medical department of a military hospital. If we again consider the kind of material — hospital patients only, in this case — too high values for tape-worm frequency might be expected as many patients admitted into hospital on account of abdominal trouble may have their symptoms caused simply by tape-worm. Seppä, however, emphasizes the fact that the soldiers' stools are generally first examined at their army detachments and that a vermifuge is administered there, a measure, that in his opinion will reduce the number of tape-worm patients in the hospitals. An other remark that might be made against Seppä's material and which seems to me more justified, is, that his investigation includes principally young men of conscript age. This may effect the result of the frequency of tapeworm anemia to some degree if we take into consideration that the disease, such as Schauman and Saltzman describe it in their statistics, occurs mostly among the 20—30 year olds, but that it is quite common at a later age, too. It occurs frequently in the forties and especially in the fifties.

On account of the remarks that may be made against Ehrström's and Seppä's material, and taking into consideration the great difference in their results, I have considered advisable to carry out a new investigation on the occurrence of pernicious tape-worm anemia in persons infested with broad tape-worm, especially as solving the question may be of great theoretical importance and perhaps of practical value, too. If Ehrström's figures are anything like correct the importance of the tape-worm as a producer of pernicious tape-worm anemia is exaggerated in comparison with that of other intestinal parasites — which he also points out in his essay. If, again, Seppä's results are correct they increase greatly the importance of the broad tape-worm as a cause of anemia of a

pernicious type. As I have been working for a year and a half, during the present war, at a place that is one of the most broad tape-worm infested places in this country, and as the war hospital to which I am attached, is the one and only hospital for the inhabitants of this place, I have had a very plentiful material at my disposal.

Material.

My material consists of civilians and soldiers admitted into the war hospital. My investigations have been carried out during a year and a half, 1. 7. 1942—31. 12. 1943. The stools of surgical patients were not as a rule examined in 1942. In 1943 practically every patient in the hospital was examined for ova of tape-worm. On this account and for other reasons, which will be dealt with further on, I have treated the material separately for the two years. I have also kept the civilians apart from the soldiers. I have, however, included the labour conscripts in the group of soldiers for the purpose of having some representatives of an older age in my material of soldiers. Lottas and nurses are included in the group of soldiers, too, though their number was extremely small in comparison with the whole material.

Results.

During the latter half of the year 1942, 850 military patients were examined in respect of tape worm. 151, i.e. 17.8 per cent of the soldiers were found to be infested with broad tape-worm. 233 civilians were examined during the same period, and 154 of them or 66 per cent were found to be infested with broad tape-worm. Some polyclinical material, comprising 273 civilians showed that 113 or 41.4 per cent were infested with tape-worm. As only those patients who showed symptoms of tape-worm were examined for ova of tape-worm — the values 17.8 per cent and 66 per cent must be considered somewhat too high. The polyclinical material, again, is too small to give any definite results.

In 1943 the stools of every patient in the hospital were examined in respect of tape-worm eggs. 2306 records were at my disposal, 1896 were of military patients and 410 of civilian patients. 275 or

14.5 per cent of the former and 245 or 59.75 per cent of the latter were infested with tape-worm. In some polyclinical material, comprising 379 civilians, 209 cases or 55 per cent were infested with tape-worm.

My investigation material was rather extensive and as almost all surgical cases were examined and as the military patients came from almost all parts of the country I may venture to say, that the value 14.5 per cent, that I have obtained, represents an almost exact fact in the Finnish army. Seppä's corresponding results support my statement. An examination of conscripts gave him the value 11.3 per cent but he takes it that this value is 2—3 per cent too low on account of anthelmintic treatment having been given in their army detachment and therefore he gives the final value of about 14 per cent. Seppä's value for the frequency of tape-worm in the army is almost the same as the value I have obtained; it may be considered a kind of approximate meanvalue, too, of the frequency of tape-worm in the whole country. There is an investigation, by Ollilainen, of a very recent date, on the frequency of tape-worm that is based upon soldier material, too. Ollilainen's values are somewhere between Ehrström's rather high values and Seppä's much lower values for the frequency in various parts of the country. As his calculations are based upon army detachments recruited almost entirely from the north of Finland he is not inclined to calculate a mean-value for the tape-worm frequency in the whole of the country.

Before considering the occurrence of tape-worm anemia in tape-worm patients, I should like to make clear in a few words, what signs each case must show before the diagnosis can be made. The anemia must be very pronounced and of an evident hypercromic type and must react favourably to the expulsion of the worm, or to liver treatment. The last mentioned therapeutics have been used in a few cases if the patients' general condition has been too low to allow a direct anthelmintic treatment.

During the latter part of 1942, 15 civilian cases of pernicious tape-worm anemia were treated in the hospital. The population of the district was at the time 8,200 and with a calculated frequency of tape-worm of 50 per cent an exact number of 4100 tape-worm carriers is obtained. Based upon these figures the frequency of tape-worm anemia is 1:273. If the frequency of anemia is calculated for the whole year the numbers of cases of tape-worm anemia ought to be at least twice the number, as a decided increase in tape-worm

anemia may generally be observed in spring and summer — Lindström points this out in his statistics. In the same half-year 29 soldiers were found to be suffering from tape-worm anemia. The calculated frequency of anemia was 1: 225 in the military material. If these values are recalculated for the whole year the frequency of anemia in civilians is 1: 136 and in soldiers 1: 113.

In 1943 decidedly fewer cases of tape-worm anemia were noticed, only in 12 civilians and in 21 soldiers. As the number of civilians in the district had increased by 1000 the tape-worm anemia frequency among them will work out at 1: 383, in other words, about $\frac{1}{3}$ of the value for the preceding year. The value 1: 241 was obtained from the military material which is about half of the value for the previous year.

Discussion.

I have obtained exceptionally high values in my investigations of the frequency of anemia in persons infested with broad tape-worm. I think, however, that they represent the true facts especially as the civilian material at my disposal must be considered most suitable for investigations of this kind. It consisted of a population strongly infested with tape-worm, and living in a limited district. All ages were represented in adequate proportions in this group of people. This material allowed me to determine almost exactly the number of cases of tape-worm anemia and to make a fairly reliable calculation of the total number of tape-worm carriers. The results obtained from the military material cannot, however, be said to be quite reliable as it has been difficult to determine exactly the strength of the forces sending patients to the hospital and consequently the total number of tape-worm carriers on which the calculations of the frequency of tape-worm anemia is, of course, based. I must, however, say that the results obtained from the military material correspond well, on the whole, with those of the civilian material. Both materials gave a considerably higher value for the frequency of tape-worm anemia than did those mentioned by Seppä. Both materials showed as well a distinct decrease in the frequency of tape-worm anemia in 1943 in comparison with the preceding year.

and in 2 syphilitic aortitis was found on autopsy. Altogether there were 68 syphilitics among the 84 cases. Of the remaining patients 8 had rheumatic aortic insufficiency, including one with Bechterew's disease who had previously suffered from rheumatic fever. All of these showed clinically and 4 also at autopsy valvular defects of the aorta only, with the exception of one who had a hemodynamically insignificant affection of the mitral valve. 3 were found on clinical examination and 2 also on post mortem examination to have aortic stenosis at the same time, of very high degree in one case (autopsy). Post mortem examination thus revealed two cases of purely rheumatic aortic insufficiency. Cabot (1) found at autopsy 6 such cases with pure aortic insufficiency among 93 patients with rheumatic aortic disease. 8 of our cases were without definite etiological diagnosis, 3 gave strong grounds for suspecting syphilis, 1 had diphtheria in the anamnesis, 1 had a severe affection of the kidneys in pregnancy, without diastolic hypertension, 1 had perhaps hypertension as basal disease. In 2 cases the aortic insufficiency seemed to coincide with aortic stenosis. One of these patients was autopsied. Thus 68 cases, or 81 per cent, were undoubtedly syphilitic, with the 3 probables 71 cases, or 85 per cent. Of the remaining 15 or 19 per cent one half were rheumatic, one half of doubtful etiology. Of the undoubted syphilitics 54 out of 68, or 79.4 per cent, had positive Wassermann (if the 3 doubtful cases are included the percentage will be 76). Sero-positive (WR or MKRII) were 62 out of 68, or 91 per cent, sero-negative 9 per cent.

Carl Müller (4) in his autopsy material of aortitis cases from Ullevål Hospital found positive Wassermann in 82 per cent, which accords well with the figures given here. By aid of Meinicke Klärung Reaktion II the sero-positivity is thus now brought up to 90 per cent.

16 of the 84 patients had normal electrocardiograms. Of left ventricular hypertrophy curves (or left retardation curves, a designation previously suggested by the author) we find 1 of type I (Fig. 1, low and isoelectric T_1 , left axis deviation), 10 of type II (lowered ST_1 , diphasic T_1), 31 of type III (lowered ST_1 , negative T_1), 6 of type IV or left b.b. block (QRS equal to or exceeding 0.12). Of the other types of electrocardiograms 5 patients had infarction curves, 1 had Wilson b.b. block, 2 atypical b.b. block, whereof one was

of anemia of pernicious type. My results stress as well the fact that the tape-worm seems to be more dangerous in times of scarcity of food.

Summary.

In 1942 the frequency of the tape-worm anemia was 1:136 and in 1943 1:383 among a population strongly infested with broad tape-worm. The corresponding figures for a material of soldiers were 1:113 and 1:241. The author is inclined to combine the higher frequency in 1942 with the difficult food conditions in that year. The scarcity or lack of Castle's extrinsic factor in food may have played an important part. The value obtained by Seppä from conscripts in peace-time, 1:659, for the frequency of tape-worm anemia in tape-worm carriers may be considered to represent the lowest possible value for the frequency in question.

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For the purpose of obtaining still more material for comparison I turned to some of my colleagues, who had worked in the same district, before the war, and requested them to let me have their opinion of the frequency of the tape-worm and of the tape-worm anemia in the district in question. According to Dr N. Wesander every second person here was infested with tape-worm and with 10—20 cases of tape-worm anemia a year the frequency of anemia is 1:300 to 1:600. According to Dr A. J. Huuskonen the tape-worm and tape-worm anemia frequency was somewhat higher. The figures for the frequency of the tape-worm anemia estimated by these two doctors lie between those I have obtained and those obtained by Seppä from a different material.

My investigations show, as seen, that the frequency of tape-worm anemia may diverge somewhat. The reason may be found in some outside factors. According to Schauman's and Saltzman's statistics professions and hygienic conditions do not seem to be the cause of tape-worm anemia to any extent. The cause must probably be sought in inadequate food. A suggestion in this direction was made by Biermer a long time ago already, in the case of cryptogenetic pernicious anemia. It lies close at hand to look for the cause of a considerable increase in the frequency of tape-worm anemia in 1942 in the food question, especially as food conditions were much better in 1943. Perhaps the increase of the frequency of the tape-worm anemia in 1942 was due to a scarcity or lack of Castle's extrinsic factor in the food. There was very little animal protein especially in the diet of the civilians in 1942. The good results in some cases of tape-worm anemia obtained by Kerppola, during this war, when using only yeast, give support to the above suggestion. Yeast is, as known, rich in extrinsic factor.

As Seppä's investigations were carried out in normal times, on selected material from the point of view of health, there is reason to suppose that his figures for the frequency of tape-worm anemia are not too high in any case. On the contrary — considering the kind of material and the time for undertaking the investigation — one might say that they are the lowest possible in theory. My values, which are considerably higher — were obtained during a time when food conditions were difficult — may in one way be considered to be the highest possible. Both results underline, however, the great importance of the broad tape-worm as a cause

Morris and his collaborators. Results with gastric juice have also, I learn, been obtained by Greenspon, Conner and Tochowicz. Carefully evaporated gastric juice of hog should, according to Morris and Tochowicz be effective too. The doses must, however, be large, i.e. a quantity of 3.2—5.7 litres of gastric juice per patient. Based upon the results of their investigations, these last mentioned authors considered that the gastric juice contains ready formed antipernicious matter. Castle and collaborators, Fouts, Helmer and Zerfas, Heinle and Miller and Ungley, Durk and Lond consider the excellent results with gastric juice due to the fact that it always contains small quantities of extrinsic factor.

Experiments have also been carried out with ventricle extract in pernicious anemia. Meulengracht and Hecht-Johansen tried to produce a preparation of hog's stomach according to the same principles as the production of liver extract for use by mouth, without obtaining any effect in one case of pernicious anemia. Wilkinson and Klein have tried to produce effective peroral extracts from hog's stomach by various methods of extracting. They did not succeed in this but obtained good results with expressed stomach juice. If the proteins in this effective preparation were precipitated the filtrate had no effect. The precipitate still contained active matter. If this matter was incubated with beef of stomach muscle a thermostabile antipernicious matter was obtained. The effective matter in the gastric wall was noticed to be very sensitive to various influences. It was never exposed to a temperature of more than 45° C at any stage. Autolysis in the presence of free hydrochloric acid, prolonged digestion with pepsin and hydrochloric acid or trypsin were injurious as well. The active principle evidently occurred in very small quantities and on this account great quantities of ventricle had to be prepared.

Wilkinson's and Klein's results, which were based upon a careful and thorough investigation, support Castle's hypothesis. This is, however, not the case in the results obtained with injectable stomach extracts. Ederle, Kriech and Gänsslen have used ventricle extract which have been produced somewhat differently to Gänsslen's liver extract. Closer explanations of the way of obtaining the extracts have not been published. With an extract of 4 g of stomach daily they obtained a clear improvement in the blood picture in pernicious anemia. These authors' investigation is of the same

time as that of Wilkinson and Klein. Aubertin's and Hector's investigation is of a considerably later date (1938). They also reached a good result in pernicious anemia with their injectable ventricle extract. They do not either give any information of the way of producing the extract but point out, that it is more difficult to obtain injectable extract of ventricle than of liver. As these results with injectable ventricle extract do not quite correspond with Castle's hypothesis and Wilkinson's and Klein's results I have considered it advisable to give an account, in short, of my experiments with injectable ventricle extracts which were carried out in 1936 and which have not for various reasons been published.

Methods.

The ventricle extracts are produced as follows. As the antipernicious substance of the stomach may be destroyed by pepsin (Greenspon, Castle, Wilkinson and Klein) but can withstand alkaline reaction (Ungley, Castle) the ground hog's stomach was extracted with an alkaline (pH 8) of 20 per cent alcohol solution at a low temperature. Low temperature and alcohol inhibit, as known, the effect of pepsin and trypsin. The extract was filtered and the remainder was treated again in the same way. Alcohol was added to both extracts which had been mixed until the mixture contained 70 per cent of alcohol. Through this procedure the proteins were precipitated almost completely. The precipitate was removed and after acidifying the filtrate it was evaporated in vacuo. As the remainder still appeared to contain protein, alcohol was added until the mixture contained 70 per cent of alcohol. After a new filtration and evaporation, and sterilized through a Seitz filter the extracts were ready for use. Altogether 7 extracts of in all 50 kg hog's stomach were produced. 5 extracts were made of stomach with the fundus removed and 2 of fundus only. The strength of the extract varied from 5 to 15 g, of stomach per ml. To ascertain that they were free from protein they were controlled with sulphosalicylic acid and that they were not toxic by tests on rabbits. The extracts have been produced for me at the medicine factory «Medica» by Mr S. Petander, Engineer, to whom I wish to express my thanks.

Results and conclusions.

The two extracts of fundus were given as intramuscular injections in one case of cryptogenetic pernicious anemia and in one case of pernicious tape-worm anemia. The former patient received altogether 100 cm³ of extract during about two weeks. The blood picture did not improve in either case. The 5 extracts of stomach

with the fundus removed were tried in 5 cases of cryptogenetic pernicious anemia and in one case of pernicious tape-worm anemia. The treatment and the size of the doses were, on the whole, the same as in the experiments with the fundus extracts. I should like to point out that the doses I used were many times larger than those given by Ederle and his co-workers. In connection with the treatment one of the patients with cryptogenetic pernicious anemia and the patient with tape-worm anemia showed a slight improvement of the blood values. The red cell count increased with about 1 million within a month, the hemoglobin percentage increased proportionally somewhat less. In the other 4 cases no increase of the blood values was observed although the reticuloocyte rose to 11 per cent in one of these 4 cases. Though I used very large doses in my experiments a moderate improvement of the blood was obtained in 2 cases only. This effect may have been caused on account of the extracts containing antipernicious matter. It may have been formed in connection with the production of the extracts in collaboration with the intrinsic and extrinsic factors contained in the stomach. The extractions were carried out, as mentioned, at a reaction of pH 8, which ought to be very favourable for the production of antipernicious matter. The results of my investigation must be considered to correspond well with Castle's hypothesis, Wilkinson's and Klein's results and Ungley's observations and thus do not support Morris', Tochowiez' and Greenspon's conceptions of the presence of ready formed antipernicious matter in the stomach. In one case of cryptogenetic pernicious anemia I administered the extract by mouth (15 g, 4 times daily) in connection with meals during 10 days. An increase of the reticuloocytes or an improvement of the blood picture was not noticed. The result corresponds with Wilkinson's and Klein's results and, as these authors pointed out the reason herefore is that the active principle of the stomach is precipitated together with the proteins.

My experiments with injectable extracts of stomach in pernicious anemia were negative whereas Ederle, Krieck and Gänsslen, and Aubertin and Hector have obtained a positive result. The favourable result obtained with their extracts may depend on the extract not being quite pure and may have contained besides small quantities of protein also active principle of the stomach.

Summary.

Experiments with injections of concentrated stomach extracts in pernicious anemia have given negative results contrary to the positive results of Ederle, Krieck and Gänsslen, and Aubertin and Hector. The extract given by mouth did not either have an effect, which may be caused by the precipitation of the active stomach principle together with the proteins (Wilkinson and Klein).

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Furthermore on the question of the pathogenesis of pernicious tape-worm anemia.

A preliminary report.

By

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(Submitted for publication May 9, 1944).

Introduction.

In a treatise on the pathogenesis of tape-worm anemia I have made myself a supporter of the conception that the pernicious tape-worm anemia appears in tape-worm carriers who have become hypersensitive to the worm. I had been able to state a decline in the blood picture in pernicious- anemic direction in persons who had previously suffered from pernicious tape-worm anemia, when they had had to take small doses by mouth of dried tape-worm whereas healthy persons and persons with cryptogenetic pernicious anemia did not seem to react in this way. v. Bonsdorff doubts, however, that my conception is correct. He bases his opinion on experiments with liver extract which has been exposed to the influence of tape-worm. He points out that when his patients received these preparations they received tape-worm substances too, which did not lessen the influence of the liver preparation, which, again, according to v. Bonsdorff, ought to have been the case, if my conception had been correct. An objection may, however, be made against this way of reasoning. In the greater number of v. Bonsdorff's cases tape-worm extracts, soluble in water, were used whereas I had thought that the tape-worm poison should be soluble in alcohol. In 3 cases only alcoholic

extracts of tape-worm were used by him in few doses and relatively small ones, in comparison with mine. Besides, the quantities of liver extract were throughout larger than those generally considered necessary for producing a remission in pernicious anemia and in pernicious tape-worm anemia without removal of the worm. v. Bonsdorff words his conception of the part played by the tape-worm in the rise of pernicious tape-worm anemia as follows:» . . . that just the occurrence of the parasite in the intestinal canal forms the most significant factor, not an indirect effect of a toxic or allergic nature.» R. Ehrström has expressed the same thought previously. If I understand v. Bonsdorff correctly, he considers, that the results of my experiments may be explained by the aid of his supposition but in which way he does not say, however. v. Bonsdorff has later investigated the effect of the tape-worm on various enzymes in human gastric juice and the presence of stomach enzymes in pernicious tape-worm anemia without yet having found a solution in this way to the question of the rise of pernicious tape-worm anemia. I have again continued along the road I started and have considered important, in the first place, to make it clear whether the tape-worm matter, principally those soluble in alcohol, administered parenterally, have the same effect as if administered by mouth. If the effect is independent of the way of administration it would speak against v. Bonsdorff's idea that the presence of tape-worm in the intestinal canal is the most significant factor but it would speak for my supposition that a resorption of tape-worm poisons are essential to give rise to pernicious tape-worm anemia. If the effect of the injected tape-worm extract is different, depending on whether or not the tested person has previously suffered from pernicious tape-worm anemia, it would again support my supposition that a variable sensitivity to tape-worm poison in tape-worm carriers plays a great part in the pathogenesis of pernicious tape-worm anemia.

Methods and Material.

Fresh, washed, broad tape-worm has been ground in a mortar to a homogenous mass with purified quartz sand. The contents of the mortar has during one week been extracted with a mixture of equal parts of ether and 96 per cent alcohol. Filtering and slow evapora-

tion of the filtrate on hot but not boiling water-bath. Suspension of the tough, dark yellowish-brown remainder in pure almond oil and sterilization in water-bath. In this suspension one gramme of almond oil has come to contain the extract of 10 grammes of fresh tape-worm. The doses have generally been 0.5 ml (= 5 g fresh or about 0.5 dried tape-worm) oil-suspension per time. This dose, administered daily, was somewhat larger than the one I used in my earlier investigation (0.3 g dried tape-worm per day). The injections have been administered intragluteally. My material comprises at present 3 «normal» cases and 2 persons just recovered from pernicious tape-worm anemia.

Results.

In my «normal» cases (1—3) the question has been of patients taken into hospital on account of troubles in the nervous system. In cases 2 and 3 broad tape-worm was found incidentally. None of these patients suffered from anemia. I purposely included cases of broad tape-worm with no anemia for the purpose of stating how the reaction of injections of tape-worm lipoids is in such a case and to be able to compare it with that of patients who had previously suffered from pernicious tape-worm anemia. — In case 1 0.5 ml of suspension of tape-worm extract were given from 2. 2. 44 to 20. 2. 44, altogether 19 injections. The hemoglobin and red cell count did not show any certain decrease during this time. The total number of white cells increased somewhat, and the eosinophiles rose from 1.5 to 7.5 per cent. In case 2 a slight decrease in the hemoglobin value and red cell count was noticed after the injections, but later both values showed a tendency to improve though the injections were continued. The number of eosinophiles increased somewhat. In this case injections of 0.5 ml were given from 8. 2. 44 to 21. 2. 44. In case 3 injections of the same kind and quantity were given almost daily during 5 weeks (13. 1. 44—20. 2. 44). During the 3 first weeks the hemoglobin decreased from 97 per cent to 85 per cent and the red cell count from 4,790,000 to 3,960,000, but both increased later as in the previous case, though the injections were continued. The eosinophiles increased successively up to 17.5 per cent. In neither case was a vermifuge given during the period of injections. Case 4 was a typical case of pernicious tape-worm

anemia which had been completely cured after a vermifuge. Soon after, from the 15.1. to the 26. 1. 44 the patient received a daily injection of 0.5 ml of *Bothriocephalus* extract pro dosi. A tenderness in the spot, where the injection was given, was noticed. It was acute in the beginning but lessened somewhat later on. The patient suffered as well sometimes from headache and chilliness. The hemoglobin value decreased with 16 per cent and the red cell count decreased with 1 million within 2 weeks. The color index and number of eosinophiles remained unchanged on the whole. On account of the quick decline of the patient's blood picture the injections were stopped, which caused the blood values to rise constantly. The starting value was reached without treatment almost within about 3 weeks. Case 5 was a patient, who had just recovered within 2 months from his pernicious tape-worm anemia after a vermifuge had been administered. He was given 15 injections of extract of 0.5 ml within 15 days. The hemoglobin decreased during this time from 101 per cent to 90 per cent and the red cell count decreased with somewhat more than 700,000. The color index rose from 1.01 to 1.07. The eosinophiles had risen from 2 per cent to 17.5 per cent. The patient did not feel well during this time and lost his appetite. For this reason the tests were discontinued. Then the red blood picture improved spontaneously within 3 weeks and the eosinophiles decreased to 5 per cent. A new test was made with tape-worm extract which had been obtained after having dissolved the alcohol-ether extract in petrolether. After the evaporation of the petrolether the remainder was suspended in almond oil. In this way a pure lipoid extract was obtained. 2 ml of this suspension was given daily during 2 weeks. The hemoglobin was reduced from 97 per cent to 94 per cent, the red cell count was reduced by 300,000. The color index increased from 1.01 to 1.04 during the same period, and the eosinophiles rose from 5.5 per cent to 10.5 per cent. The test was discontinued at this point as the patient had to leave the hospital for various reasons.

Comments.

In one of the «normal» cases no decrease in the blood values was noticed during the time the tapé-worm extract was administered. In the other 2 cases the values decreased in the beginning but increased later though the injections were continued. A simil-

ar case was observed by Nyfeldt in his tests on animals with Bothriotoxin. When using constant doses the changes in the blood picture disappeared gradually; only by the aid of continually increased doses did he succeed in causing a severe anemia of hypercromic type in his test animals. There is much that points to the case being similar in persons. Tallqvist thus caused in himself a distinct hypercromic anemia when taking increasing doses of tape-worm lipoids by mouth. In my 2 cases in which a pernicious tape-worm anemia had occurred shortly before, the case seems to have been somewhat different. In both cases a greater decline in the blood picture than in that of the «normal» cases was observed after the use of constant doses of tape-worm extract and the blood did not improve until the injections were discontinued. The injections were stopped as the two patients felt ill and lost their appetite at the same time on account of the rather sudden decline of the blood picture. In 3 of the cases, i. e. the one that had suffered from tape-worm anemia and 2 of the «normal» cases a strong increase of the eosinophiles was noticed during the time tape-worm extract was administered. They decreased rapidly again when the injections were stopped. Perhaps there is in this a certain evidence that the tape-worm poisons administered were genuine. Tape-worm infestation often leads to eosinophilia, as known. A moderate increase of the sedimentation reaction was noticed in all cases as long as the extract was given to the patients.

The result of this investigation corresponds on the whole well with the results obtained in my previous investigation with constant small doses of dried tape-worm or alcohol-extract given by mouth. In both cases a decrease of the blood values was noticed in persons who had suffered from tape-worm anemia previously. These blood changes were quickly cured when the tape-worm preparations were stopped. The passing decline of the blood picture that was noticed in some of the normal persons after tape-worm extract injections had been given, was not noticed at all when dried tape-worm and an alcoholic extract of it were administered by mouth. This might perhaps mean that tape-worm matter was not resorbed, without hinderance, into the blood stream, in all circumstances. This conception is also supported by the results, obtained by Sievers, when examining the material of my previous investigation. He discovered tape-worm antibodies in a greater number

of patients who had previously suffered from tape-worm anemia or who suffered from cryptogenetic pernicious anemia than in other persons. These observations may give a certain support to the idea maintained by Seyderhelm among others, of an increased permeability of the intestinal canal in pernicious anemia. It cannot, however, be a decisive factor in pernicious tape-worm anemia as all persons should then have to react in the same way to the injections of tape-worm particles and my investigation shows clearly that this is not the case. The result of my investigation supports the supposition I have expressed before that a hypersensitivity to the tape-worm plays an essential rôle in the pathogenesis of pernicious tape-worm anemia.

Summary.

An alcohol-extract of broad tape-worm administered parentally in constant doses caused, in two persons who had suffered from pernicious tape-worm anemia, a clear decline in the blood picture which improved spontaneously only when the preparation was left off. Some local and general symptoms were observed as well. A control person did not show any changes, 2 others a passing decline in the blood picture which improved, however, though the preparation was continued. According to the author, these results support the conception, expressed previously, that an increased sensitivity to tape-worm poison plays an important rôle in the pathogenesis of tape-worm anemia.

Cases.

Case 1. Soldier, 23 years. Dg. Enuresis nocturna. 1. 2. 44. Hb 81/94, E. 4,490. I 1.04, L. 5,400, Eosin. 1.5, Rod forms 1.5, Polymorph. neutr. 50, Lymph. 35, Monoc. 12. 5. 2. 44. Hb 79/92, E. 4,310. I. 1.06, L. 6,400, Eosin. 2.5, Rod forms 3.5, Polymorph. neutr. 55.5, Lymph. 29, Monoc. 9.5, 9. 2. 44. Hb 83/96, E. 4,600. I. 1.03, L. 9,200, Eosin. 3.5, Rod forms 4, Polymorph. neutr. 61, Lymph. 23, Monoc. 8.5, 17. 2. 44. Hb 80/93, E. 4,410. I 1.04, L. 8,200, Eosin. 7, 5, Rod forms 5, Polymorph. neutr. 55.5, Lymph. 23, Monoc. 9. 23. 2. 44. Hb 82/95, E. 4,500. I. 1.04, L. 8,100, Eosin. 7.0, Rod forms 3.5, Polymorph. neutr. 57.5, Lymph. 25, Monoc. 7.

Case 2. Farmer, 38 years. Dg. Syndroma ischiad. *Diphyllbothrium latum* 8. 2. 44. Hb 90/104, E. 5,070. I. 1.02, L. 3,560, Eosin. 5, Polymorph.

neutr. 54, Lymph. 33, Monoc. 8. 15. 2. 44. Hb 83/96, E. 4,636. I. 1.03, L. 7,200, Eosin. 2, Rod forms 2.5, Polymorph. neutr. 68.5, Lymph. 23.5, Monoc. 3.5. 22. 2. 44. Hb 85/99, E. 4,710. I. 1.05, L. 6,200, Eosin. 6.5, Rod forms 2, Polymorph. neutr. 57.5, Lymph. 26, Monoc. 8. 29. 2. 44. Hb 86/100, E. 4,950. I. 1.01, L. 4,400, Eosin. 5.5, Rod forms 1, Polymorph. neutr. 57, Lymph. 32.5, Monoc. 4.

Case 3. Labourer, 39 years. Dg. Debilitas. *Diphyllbothrium latum*. 10. 1. 44. Hb 84/97, E. 4,790. I. 1.01. 17. 1. 44. Hb 79/92. E. 4,570. I. 1.01. 21. 1. 44. Hb 80/93. E. 4,440. I. 1.05. 25. 1. 44. Hb 81/94. E. 4,450. I. 1.06. 31. 1. 44. Hb 73/85. E. 3,960. I. 1.07, L. 7,300, Eosin. 7. Basophil. 0.5, Rod forms 1.5, Polymorph. neutr. 52.5, Lymph. 26.5, Monoc. 12.12. 4. 2. 44. Hb 80/93, E. 4,430. I. 1.05, L. 5,000, Eosin. 8, Rod forms 2, Polymorph. neutr. 55, Lymph. 30.5, Monoc. 4.5. 10. 2. 44. Hb 79/90, E. 4,110. I. 1.12, L. 6,200, Eosin. 9.5, Basoph. 1, Rod forms 3.5 Polymorph. neutr. 49.5, Lymph. 30.5, Monoc. 6. 14. 2. 44. Hb 80/93, E. 4,130. I. 1.12, L. 6,300, Eosin. 11.5, Basoph. 0.5, Rod forms 0.5, Polymorph. neutr. 50.5, Lymph. 31, Monoc. 6. 21. 2. 44. Hb 82/95, E. 4,530. I. 1.05, L. 5,200, Eosin. 17.5, Basoph. 0.5, Rod forms 2, Polymorph. neutr. 42.5, Lymph. 30, Monoc. 7.5.

Case 4. Farmer, 41 years. Dg. Status p. anæmiā perniciosā diphyllobothricā. 14. 1. 44. Hb 86/100, E. 4,920. I. 1.02, L. 3,400, Eosin. 8.5, Basoph. 1. Rod forms 0.5, Polymorph. neutr. 50, Lymph. 35, Monoc. 5. 20. 1. 44. Hb 83/96, E. 4,600. I. 1.04, 24. 1. 44. Hb 76/88, E. 4,220, I. 1.04, 27. 1. 44. Hb 72/94, E. 3,940. I. 1.06, L. 5,400, Eosin. 5, Rod forms 4; Polymorph. neutr. 57, Lymph. 32.5, Monoc. 1.5. 22. 1. 44. Hb 73/85, E. 4,060, I. 1.05, L. 4,900, Eosin. 7.5, Basoph. 0.5, Rod forms 4, Polymorph. neutr. 55.5, Lymph. 28, Monoc. 4.5, 9. 2. 44. Hb 78/90, E. 4,310, I. 1.04, L. 3,900, Eosin. 4.5, Basoph. 1.5, Rod forms 1, Polymorph. neutr. 52, Lymph. 39, Monoc. 2. 14. 2. 44. Hb 82/95, E. 4,590. I. 1.03, L. 3,000, Eosin. 7, Basoph. 0.5, Rod forms 1.5, Polymorph. neutr. 50, Lymph. 40, Monoc. 2. 21. 2. 44. Hb 86/100, E. 4,840, I. 1.03, L. 4,700, Eosin. 5.5, Basoph. 1, Rod forms 1, Polymorph. neutr. 50, Lymph. 37.5, Monoc. 5.

Case 5. Labourer, 24 years. Dg. Status p. anæmiā perniciosā diphyllobothricā. 12. 1. 44. Hb 87/101, E. 4,960. I. 1.01, L. 6,800, Eosin. 2, Basoph. 0.5, Rod forms 2, Polymorph. neutr. 56.5. Lymph. 27.5, Monoc. 11.5. Injections 14. 1. 44.—28. 1. 44. 17. 1. 44. Hb 88/102, E. 4,950. I. 1.03, 21. 1. 44. Hb 85/99, E. 4,860., I. 1.02, 25. 1. 44. Hb 82/95, E. 4,570. I. 1.04, 29. 1. 44. Hb 78/90, E. 4,220. I. 1.07, L. 8,600, Eosin. 17.5, Basoph. 2.5, Rod forms, 2.5, Polymorph. neutr. 50, Lymph. 19.5, Monoc. 8. 1. 2. 44. Hb 80/93, E. 4,340, I. 1.07, 4. 2. 44. Hb 80/93, E. 4,320 I. 1.07, L. 7,500, Eosin. 10.5, Rod forms 1.5, Polymorph. neutr. 57.5, Lymph. 25, monoc. 4.5. 9. 2. 44. Hb 80/93, E. 4,330. I. 1.07, L. 6,800, Eosin. 8, Rod forms 1.5, Polymorph. neutr. 60, Lymph. 23.5, Monoc. 7. 21. 2. 44. Hb 84/97, E. 4,820, I. 1.01. L. 7,700, Eosin. 5.5, Rod forms 0.5, Polymorph. neutr.

56, Lymph. 27, Monoc. 11. Injections of purified extract 22.2.—6. 3. 44. 28. 2. 44. Hb 84/97, E. 4,800. I. 1.01, L. 8,700, Eosin. 4.5, Basoph. 2.5, Polymorph. neutr. 61, Lymph. 24, Monoc. 8. 6. 3. 44. Hb 81/94, E. 4,520. I. 1.04. L. 6,800, Eosin. 10.5. Rod forms 1.5, Polymorph. neutr. 56, Lymph. 28.5, Monoc. 3.5.

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From the Medical Out-patient Department of the Rigshospital, Copenhagen
(Director: Professor Eggert Møller, M.D.).

Serum Copper. V. Thyrotoxicosis and Myxoedema.

By

A. LEVIN NIELSEN.

(Submitted for publication April 28, 1944).

In 1932 Locke and collaborators (2) called attention to the observation that increased metabolism and fever may be associated with a rise in the serum copper concentration, while serum copper was not lowered to any particular extent in an untreated myxoedema patient. Especially Narasaka (3—6) has investigated the influence of the thyroid gland on the copper content of whole blood. For determination of copper he employed Sarata's (8) method, with which technique he (6), like Sarata, (9) found considerably lower normal values for human serum than reported by other investigators.

As this difference in the values obtained must be due either to differences in the human material examined or, more likely, to discrepancies of analytical nature, one naturally is at a loss in judging of these investigations. Narasaka found that the copper content of the blood in normal rabbits is increased by administration of thyroid and decreased by thyroidectomy, and in the latter case the blood copper can again be brought up to a normal level or even higher by oral administration of thyroid. In 4 patients suffering from exophthalmic goiter Narasaka (6) found the copper content of whole blood to be above the normal level; he examined no case of myxoedema.

Finally, Heilmeyer (1) and collaborators have determined the serum copper concentration in 4 patients with hypothyroidism and 17 with thyrotoxicosis and found that presumably there is a certain connection between increased metabolism and increased serum copper concentration.

On this background the following studies were carried out.

The analytical technique was the same as described previously (7). The analyses were always carried out in duplicate and analyses with a difference in the two results exceeding 3 % are not taken into account. The patients were not fasting when blood was withdrawn for this analysis.

All the present patients come from the Medical Out-patient Department of the Rigshospital, where they were under ambulatory treatment or admitted to the stationary clinic of this department for medical treatment aiming at operative treatment. The present studies comprise 42 patients with thyrotoxicosis, 3 with myxoedema.

Of the 42 cases of thyrotoxicosis 11 have been left out from the present account because of concomitant infection (sinusitis in 3 cases, cold in 3, periodontitis in 2, skin lesions in 2, purulent rhinitis in 1), while none of the myxoedema cases has been left out.

On the basis of the outcome of the determinations of the metabolism, which were performed very often in each case, the 31 cases of thyrotoxicosis are divided into 3 groups after the degree of the disease. This estimation of the case was based on the first two determinations which did not differ over 5 % — in a great majority of the cases obtained before the institution of the iodine therapy. The mildest cases are defined as cases in which the average of the first two determinations does not exceed 135 % (10 patients); a moderate degree of the lesion comprises patients with a metabolic rate of 135—155 % (5 patients), while the remaining patients represent a severe degree (16 patients). Of the last-mentioned 16 patients 10 constitute a special group by themselves, as they could not be rendered operable under a previous hospital treatment, so that in these cases the serum copper determination has been carried out during a subsequent hospitalization.

In Fig. 1 a graphical presentation is given of comparison between the first serum copper determination and the simultaneous

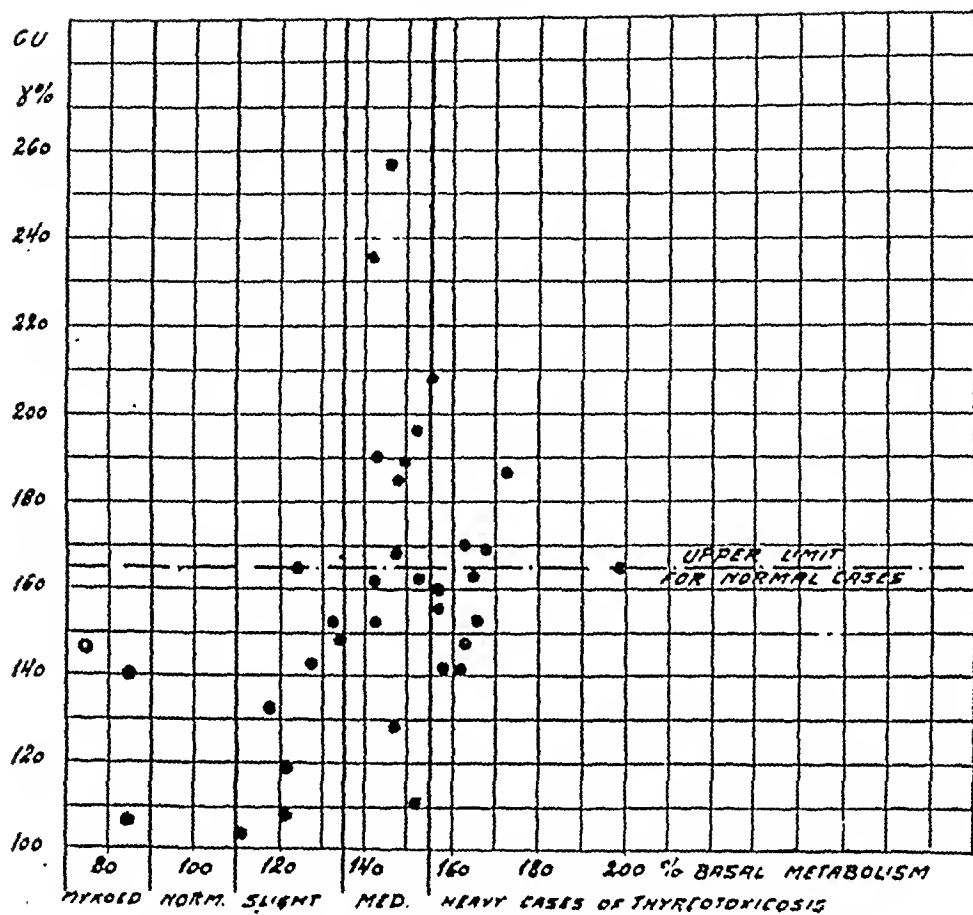


Fig. 1. Comparison between metabolism and serum copper.

basal metabolism in the 34 patients. While the serum copper values are normal in the cases of myxoedema and in the mildest cases of thyrotoxicosis, the serum copper in the moderate and severe cases of thyrotoxicosis is often increased, though without showing any particular connection between the height of the metabolism and the serum copper level. Postoperative reexamination of 7 patients residing in Copenhagen gave the results presented in Fig. 2. Of these 7 patients 6 were well, 1 had a relapse. All showed a lower rate of metabolism and lower serum copper. It thus seems reasonable to assume a connection between the thyrotoxic increase in metabolism and the increase in serum copper. Attempts were made to find some relation between the variations in the metabolism and serum copper during the course of illness in the individual patients, but no such connection could be demonstrated

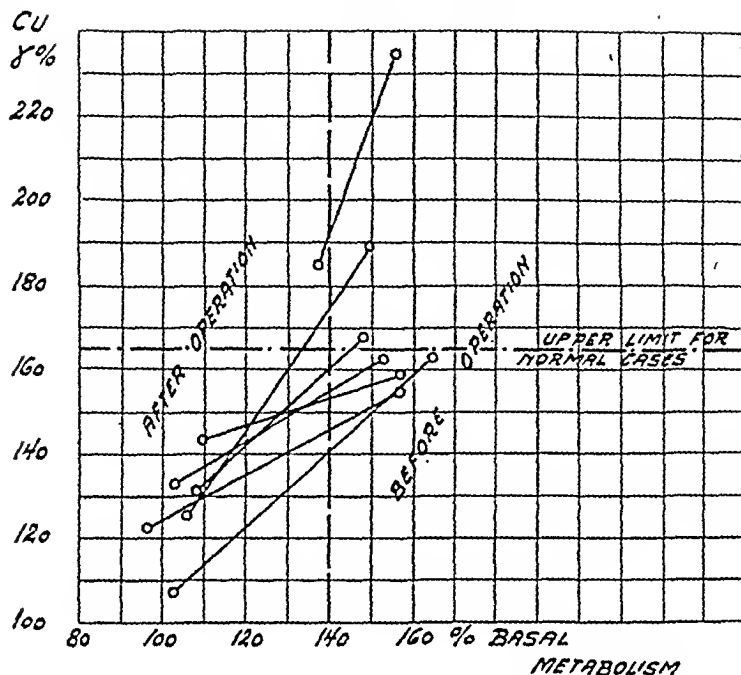


Fig. 2. Comparison between serum copper and metabolism before and after the operation.

even with merely a fair degree of regularity. Nor could any connection be demonstrated between the increase in sedimentation rate and the two other values.

So we have to conclude that in thyrotoxicosis the serum copper concentration is normal in mild cases, while it is often increased in the more severe cases. In 3 cases of myxoedema the values for serum copper were decreased within the normal limit.³

Summary.

On determination of serum copper on 31 patients with thyrotoxicosis values increased above the normal were found in some of the moderate and all the severe cases.

Reexamination of 7 patients operated on for thyrotoxicosis showed normal metabolism and serum copper in 6, while 1 still presented an increased metabolism and increased serum copper.

It is not possible to demonstrate a regular connection at any point of time between the increase in metabolism and the rise in serum copper.

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Primary and Secondary Xanthomatosis.

By

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(Submitted for publication May 2, 1944).

The literature on xanthomatosis is, by its many isolated cases, apt to give the reader the impression that the disease is a relatively rare one. The impression is different, however, when taking into account the papers published by Thannhauser and Magendanz (United States) and Müller (Norway) where a very considerable material is presented; especially as the material of Müller appears to have been collected in a very short time. The explanation must be that the disease is not unusual, but that it is diagnosed far too infrequently. This is confirmed by the fact that in 3 years at the Medical Policlinic of Rigshospitalet, Copenhagen, 11 cases of xanthomatosis have been diagnosed (this diagnosis being in most instances the main diagnosis) without any special search being made for such patients.

The xanthomatoses, together with Gaucher's disease and Niemann-Pick's disease, belong to the lipidoses. They are classified as follows:

- | | |
|------------------------------|-------------------------|
| Lipidoses: Gaucher's disease | (cerebroside) |
| Niemann-Pick's disease | (sphingomyelin) |
| Xanthomatosis | (cholesterol) |
| | a. Primary (idiopathic) |
| | b. Secondary |

Associated are:

- Cholesterol deposits in a) granulation tissue (especially Schüller-Christian's syndrome)
b) tumors.

In xanthomatosis the cholesterol is found to be characteristically deposited in cells which in ordinary preparations have a foamy appearance, and which in frozen sections show typical double refraction as a sign of the presence of cholesterol. There has been a tendency to consider all diseases, which histologically are characterized by the presence of these cells, as xanthomatosis. It is possible, however, from this group to segregate a series of clinical entities, so that there remains a uniform rest which must be designated as primary, idiopathic xanthomatosis. It is this disease which must be placed in the same class as the other forms of lipidosis, although in certain essentials it seems to constitute another form of metabolic abnormality. The following will mainly deal with this primary, idiopathic xanthomatosis.

Secondary xanthomatosis must be considered as distinct from the primary ones. The cholesterol deposits appear in consequence of a hypercholesterolemia of other known cause such as, for example, diabetes mellitus. Both in their histological aspects and in their progress and treatment the secondary xanthomatoses will differ from the primary ones.

As a third group may be mentioned Schüller-Christian's disease. In the past, most attention has been given to the frequent occurrence of cholesterol in the characteristic granulation tissue, and the disease has been classified as a typical xanthomatosis. Thus Thannhauser designates it as primary xanthomatosis of normocholesterolemic type. However, an increasing number of cases are reported in which not a single typical cholesterol-containing cell is found in the granulation tissue, wherefore this disease must now be regarded as having a different origin.

Primary Xanthomatosis.

The material comprises 8 cases of primary xanthomatosis; they are arranged according to visible symptoms. First, some patients with xanthelasmata and flat xanthomata.

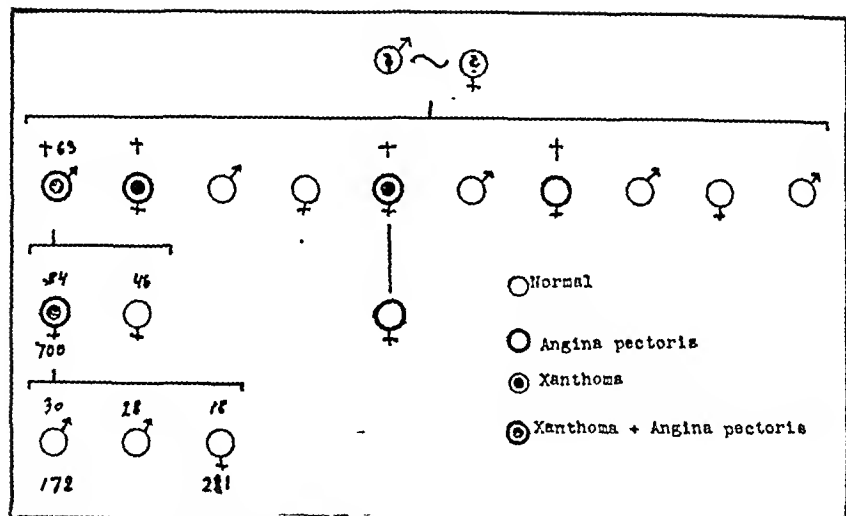


Fig. 1. The figures above the circles indicate the age, the figures below indicate the serum cholesterol.

Case No. 1. Woman aged 54. Fig. 1 records the family history. In all essentials the patient was well until the present disease began in 1931 in connection with an abortion. Since then she had typical angina pectoris with precordial pain radiating to the arm when she was at work. The patient was treated with nitroglycerin, with good results. Yellow plaques at the eyes since 1920. The plaques were removed at the Finsen Institute shortly after, but reappeared and are now constantly growing. During recent years there moreover appeared a yellow plaque beneath the wedding ring. The patient's hypercholesterolemia was discovered in 1941, and was then 595 mg %. She has been kept on a diet poor in cholesterol, but the serum cholesterol value remained above 500 mg % all the time, and was in periods up to 700 mg %. The last examination showed 600 mg %.

Physical examination showed typical xanthelasmata as circles around both eyes. Similar xanthomata were observed on the creases of the 3rd finger of the right hand. On the flexor tendon of the 2nd finger of this hand a hard nodule could be felt. Otherwise nothing of interest. Blood pressure 150/70. The electrocardiogram always normal. X-ray examination of the heart showed nothing abnormal except calcification of the arch of aorta. The peripheral arteries showed no lime deposit. Oscillometry of the legs gave but small deflection, not over 1 unit.

Case No. 2. Woman aged 54. The patient was referred to the Polyclinic for examination of the heart before a gynecological operation. Past history of good health, except for cystitis and gastric catarrh. The patient never had angina pectoris, but was during the last 2 years troubled with a little breathlessness. For a number of years she has had xanthelasmata at both eyes.

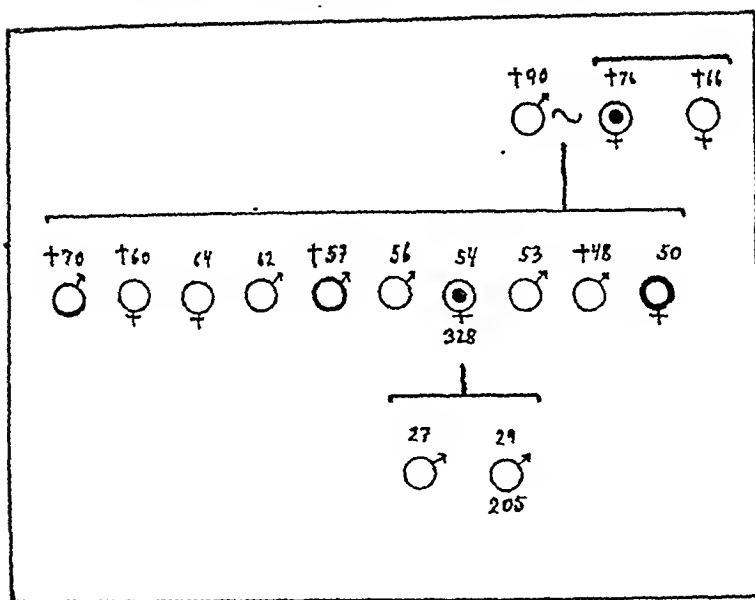


Fig. 2.

Physical examination showed 3×55 mm large xanthelasmata medially at both upper eyelids. Otherwise nothing abnormal, except some varicose veins. The serum cholesterol value was found to be 328 mg %. X-ray examination of the heart, and the electrocardiogram showed normal conditions. Blood pressure 110/80. Fig. 2 records the family history.

Case No. 3. Woman aged 24. Her mother died rather young from angina pectoris; otherwise no known heart disease in the family. The patient is the first to show skin symptoms. When 12 and 18 years of age she was admitted to Sct. Mariae Hospital in Roskilde, with rheumatic fever. The second time she was treated with sanocrysin. Remnants of the disease are still found in the joints of the fingers. A couple of months after being discharged the second time she developed a skin disease on the buttocks and the thigh. Otherwise no complaints. In 1940 the skin disease was treated at the Dermatological Clinic of Rigshospitalet where biopsy disclosed xanthomatosis. Since then the skin disease has spread to the anterior left thigh.

Physical examination showed nothing abnormal beyond two irregular yellow plaques, somewhat larger than a hand, on the buttocks extending down on the thigh, as well as a similar, approximately 5×7 cm large affection of the anterior left thigh. Serum cholesterol value 371 mg%. X-ray examination of the heart, and the electrocardiogram, showed normal conditions. Blood pressure 120/80.

Case No. 4. Woman aged 67. Family history unknown. Past history of good health. During the last couple of years she had several attacks of

precordial oppression when exerting herself. The attacks disappeared immediately when she stood quiet. The last few days before coming to the Policlinic she suffered from constant oppression and palpitation of the heart.

Physical examination showed rapid auricular fibrillation and a pulse deficit of about 40 %. Moreover, pronounced arcus senilis and xanthelasmata at both upper eyelids. Serum cholesterol value 308 mg %. X-ray examination of the heart showed hypertrophy of the left ventricle, without visible calcification in aorta. Blood pressure 180/90.

The next group includes some patients with tendinous xanthomata.

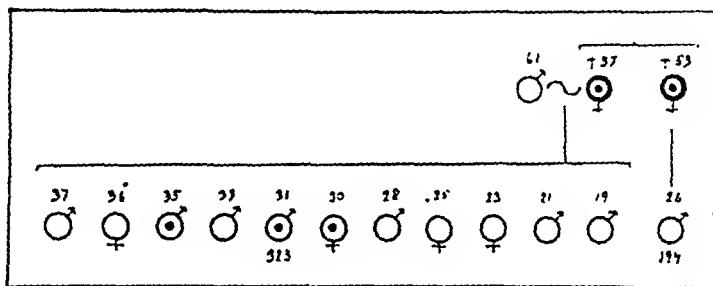


Fig. 3.

Case No. 5. Man aged 31. Fig. 3 records the family history. Aside from a period 3 years ago, with symptoms of ventricular ulcer, the patient has been of good health. During the last 10 years there have been nodules on the extensor sides of both hands, on wrist and on elbow. Some years ago he had similar nodules removed from wrist and elbow, but later new ones developed, of which those on the wrist appeared at the places of the sutures from the first extirpation. Otherwise no complaints.

Physical examination showed $2 \times \frac{1}{2}$ cm large, rather firm, indolent nodules on all tendons of the knuckles. On the extremity of the 5th finger of the right hand was a pea-size yellow nodule. On the right elbow and on both side of a cicatrix on the right wrist there were observed pea-size yellowish cushions. Moreover, a pea-size yellow nodule on the right cheek. Otherwise nothing abnormal. X-ray examination of the heart, and electrocardiogram showed normal conditions. Serum cholesterol value 323 mg %.

Case No. 6. Woman aged 29. The mother had angina pectoris, otherwise no data regarding the health of the family. The patient had 4 attacks of rheumatic fever, at the age of 16 years with possible cardiac complications. When about 17 years old a nodule developed on the right and left 3rd finger, in connection with a lesion. Later there appeared nodules on the right knee and the right Achilles' tendon, as well as on the left 4th

finger. These nodules, except the one on the 4th finger, were removed in 1941. Since then no new nodules have appeared.

Physical examination showed nothing abnormal except a bean-size nodule on the left 4th finger. Examination of the heart showed nothing abnormal. The serum cholesterol value was: 1941, 447 mg %—1943, 394 mg %.

Case No. 7. Man aged 32. 4 to 5 years ago indolent nodules developed on the dorsal side of the hands. Since then they increased in number and size, and similar nodules appeared on the heels. In 1941 admitted to the Surgical Polyclinic where the nodules on the heels and one on the right wrist were removed. Otherwise no complaints — especially no heart disease.

Physical examination showed typical bean-size nodules over the knuckles of both hands, localized to the extensor tendons. Similar nodules were observed on both elbows and on the Achilles' tendons. No xanthelasmata. Serum cholesterol value: 1941, 416 mg %—1942, 591 mg %.

Finally, a patient in whom there was nothing visible to support the diagnosis:

Case No. 8. Man aged 37. Fig. 4 records the family history. He had influenza when 14, otherwise of good health. During the last 2 years prior to the examination the patient suffered from typical attacks of angina pectoris when exerting himself. Was treated with nitroglycerin with good effect. In 1941 the patient was admitted to the Stationary Ward of the Polyclinic because of his heart disease.

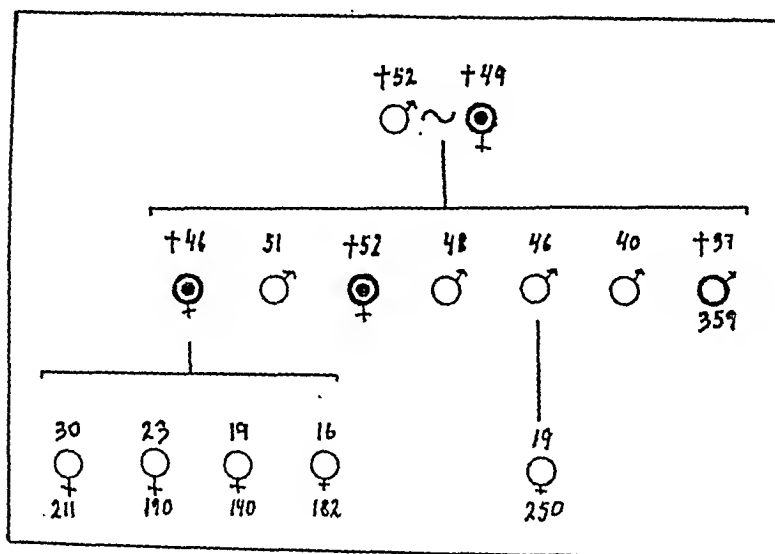


Fig. 4.

Physical examination showed nothing abnormal, especially no xanthelasmata or tendinous xanthoma. Blood pressure 125/90. Electrocardiogram showed T₁ negative, otherwise nothing of interest. X-ray examination of the heart showed normal conditions. Oscillometry of crus showed maximum deflections of 2—3. X-ray examination of the legs disclosed calcification of the arteries. Serum cholesterol value 359 mg %.

During the ensuing years the patient came to the Polyclinic because of constipation and dyspepsia. His angina pectoris was unchanged. On September 23, 1943 he was brought dead to Rigshospitalet, following bodily exertion. Unfortunately, no autopsy was performed.

Table I.

The occurrence of xanthomatous manifestations and angina pectoris in the patients and their families.

No.	Sex	Age	Xanthelasmata		Tuberous xanthomata		Tendinous xanthomata		Arcus senilis	Angina pectoris		Serum Chol. mg %	Blood Press.
			Pt.	In the family	Pt.	In the family	Pt.	In the family		Pt.	In the family		
1	K	54	+	+	—	—	+	?	—	+	+	700	150/70
2	»	54	+	+	—	—	—	—	—	—	+	328	110/80
3	»	24	+	—	—	—	—	—	—	—	+	371	120/80
4	»	67	+	?	—	?	—	?	+	+	?	308	180/90
5	M	31	—	—	+	—	+	+	—	+	?	323	115/70
6	K	29	—	—	—	—	+	—	—	—	+	447	120/80
7	M	32	—	?	+	?	+	?	—	—	?	591	119/70
8	»	37	—	—	—	—	—	—	—	+	+	359	125/90

The most important symptoms and their incidence are recorded in table 1. It will be seen that the clinical picture is well defined and uniform, and, more especially, that the same group of symptoms reappear in the patients' families.

If we are to discuss the symptoms singly it is most reasonable to begin with the *cholesterol level*. The analyses are made according to Georg C. Bruun. In all cases examined the level has been above 300 mg %, which, by the method used, should place it definitely above the normal level. Unfortunately, the upper limit for the serum cholesterol level in normal individuals has not yet been fully established. One reason is that the different methods employed have given rather different results. Another reason is that it must be assumed that in a material comprising apparently nor-

mal individuals there may be found members of xanthomatosis families where the xanthomatosis has not yet become manifest. In a disease so distinctly hereditary, where the first symptoms frequently do not appear until the individual is 40 to 50 years of age, it should be reasonable to think that some younger people would not reveal their xanthomatosis till later and therefore appear normal except for their hypercholesterolemia. That this is actually so is shown very clearly, for example, by the genealogical table published by Svendsen. Here we find one member with manifest xanthomatosis, but several of the family undoubtedly have increased values and several show high normal values. It is interesting to see that the highest values are found among the older members of the family. In the young even the higher values lie but little above normal.

Entirely similar observations have been made by Thannhauser and Magendantz. In one case they found the serum cholesterol value to increase at the same time as there appeared manifestations of an otherwise hereditary xanthomatosis. Hence one should with interest consider a case like that of the 19 year old woman (fig. 4) with a serum cholesterol value of 250 mg %, and the 18 year old woman (fig. 1) with a serum cholesterol value of 250 mg %, and perhaps observe these patients over a period of years in order to learn whether such patients later on will develop manifest xanthomatosis with hypercholesterolemia. Another genealogical table of a family with hypercholesterolemia but without clinical xanthomatosis has been published by Kornerup; it is similar to those mentioned. According to this table, as in that published by Svendsen, the hypercholesterolemia appears to be hereditarily dominant.

Thus when selecting a normal material for determinations of serum cholesterol it is a necessary requirement, in addition to what is otherwise required of a normal material, that there are no visible manifestations of xanthomatosis in the family, and no cases of angina pectoris or sudden death from heart failure. Kornerup presents a material of this kind. He finds the highest normal serum cholesterol values to be 320 mg %; nevertheless, he considers values above 300 mg % as definitely increased.

For the purpose of elucidating conditions in individuals who must be supposed to be non-carriers of this hereditary hyper-

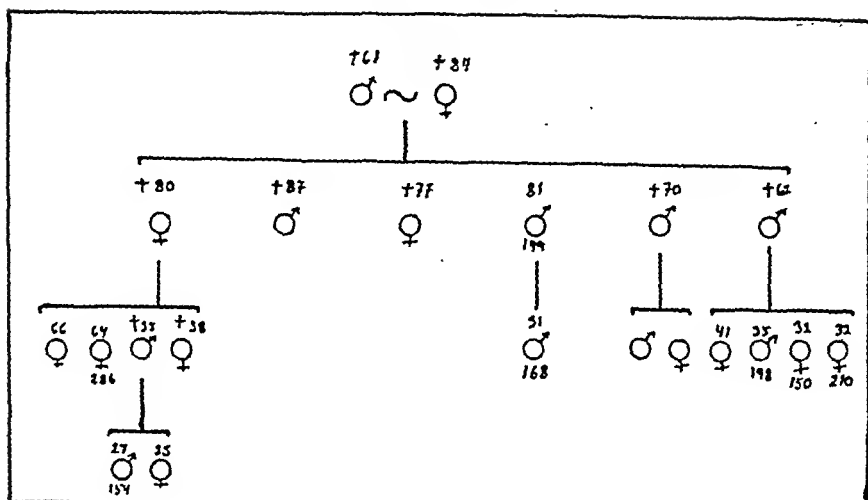


Fig. 5.

cholesterolemia, the present author has examined a family where all the individuals who have not died from incidental diseases have reached an age of more than 80 years without showing signs of arteriosclerotic heart trouble. This family (see fig. 5) shows in nearly all cases examined a serum cholesterol value below 200 mg %.

The *cutaneous manifestations* have been mentioned in detail when describing the various cases. It is here a question of either flat or tuberosus xanthorrata. They are pathognomonic of the disease, unless they appear as typical small xanthelasmata at the eyelids. In patients with the latter symptoms the serum cholesterol value is frequently found to be normal. The author has examined two such cases with values of 175 and 208 mg %. Peculiarly enough, the mothers of both patients had similar xanthelasmata. That some patients nevertheless may have an increased serum cholesterol percentage is evident from the paper by Kornerup where he finds values up to 500 mg %.

The *tendinous xanthomata*, which are found sometimes as soft and sometimes as hard nodules on the tendons, are likewise pathognomonic. They seem to appear especially on the extensor tendons of the fingers, on tuberositas tibiae and on the Achilles' tendons. They undoubtedly are apt to occur after minor lesions, as in the above mentioned case No. 6. The same is probably true of the

flat xanthomata. In case No. 1 we find such a xanthoma beneath the wedding ring, in No. 3 on the buttocks; case No. 5 has developed tuberous xanthomata in the grooves left from the suture after extirpation of a xanthoma.

A special form of cholesterol deposit is observed in *arcus senilis*, and in several instances this disease has been described as a manifestation of xanthomatosis. Ehlertsen describes a family in which the phenomenon is observed, and the above mentioned case No. 4 falls within the category. It has long been known that there is a connection between arcus senilis and arteriosclerosis (Strömberg), but a closer understanding is first obtained by the observation just cited.

In addition to the visible deposits there are also found deposits in various organs of the body, and it is these deposits which are of special interest to the clinician. We are first of all concerned with changes in the blood vessels and the bile ducts.

The vascular deposits should undoubtedly be considered as of the very highest importance. Actually they have been known for long, and there have been published several reports on fatal cases of arteriosclerosis, especially with coronary disease, in young patients who were xanthoma carriers (Harbitz, Arning, Hess). However, it is not until the publications by Müller from 1939 that it has been made clear how significant this connection is. An examination of the material contained in the present paper will show that it corresponds to that presented by Müller. The genealogical tables, figs. 1—4, show how frequently a fatal arteriosclerosis with angina pectoris is found among the relatives of the patients. It is moreover striking how low the age is in the case of these deaths. In 8 instances the age is known; of these eight patients one died when less than 40 years of age, two at the age between 40 and 50, and four at less than 60 years of age. To this should be added two cases of sudden death by heart failure in xanthomatosis at the age between 40 and 50 years. Autopsy was performed in these two cases, and data will be given in a later publication.

The cause of these heart attacks is the xanthomatous deposits in the intima of the blood vessels. The changes, which are found especially in aorta and in the coronary arteries, are macroscopically of exactly the same appearance as a very severe arteriosclerosis. Hoffmeyer has described the histological details on the basis of

a case of severe xanthomatosis. He finds, like Müller, that it is impossible to differentiate between the xanthomatous arteriosclerosis and arteriosclerosis of other origin. It seems, though, that the xanthomatous blood vessels contain more foam cells than ordinarily found in the usual form of arteriosclerosis. More particularly, the foam cells are found diffused in the wall of the vessels and not only in the margin of the atheromatous plaques. Thus it appears as if the xanthomatosis were capable of promoting the atheromatous transformation of the vessels so that it may be highly developed in very young individuals.

A circumstance that deserves to be mentioned is the small frequency of hypertension among the xanthomatosis patients, even when they suffer from severe arteriosclerosis. Thus among the author's patients only No. 4 has hypertension. Nor do patients with essential hypertension appear to have hypercholesterolemia.

The other internal localization of the xanthome nodules is in the *bile ducts*, especially in the larger ones. The author has had no patients with this clinical picture of the disease and must refer to Thannhauser and to Riisfeldt-Pedersen. The xanthomatous nodules give rise to bile stasis, which frequently is incomplete, but may persist for many years. It is often followed by a biliary cirrhosis where at the same time ample amounts of cholesterol are deposited in the liver. As long as the stoppage of the bile flow prevails, the patients' hereditary hypercholesterolemia will be further accentuated by the rise which is frequently observed in obstructive jaundice. The result is extremely high serum cholesterol values — as much as 1500 mg % being not unusual.

There are also on record xanthomatous changes in pancreas, resulting in diabetes mellitus. Apart from these deposits there seem to be no instances of primary xanthomatosis in other organs.

The treatment of primary xanthomatosis is as yet uncertain. In the case of individuals showing hereditary increased serum cholesterol values it is undoubtedly well to prescribe a diet poor in animal sterols, *i.e.*, without milk, butter, cheese and animal fat, while margarin of vegetable origin may be permitted. Only few patients will adhere to such a diet, and, besides, the result is doubtful. In the author's material the diet has been tried for years in the case of patient No. 1, but appears only to have been effective during the period of hospitalization. Easier to carry out, but at the same

time more risky, is a thyroid treatment. This treatment has been attempted, on the ground that when hyperthyroidism is accompanied by low values of the serum cholesterol it might perhaps be possible to reduce an increased serum cholesterol value by increasing the metabolism a little through administration of thyroid. This has been tried in the above mentioned case No. 5, but results are not yet available.

Secondary Xanthomatosis.

In several respects the secondary xanthomatoses show an entirely different picture from that of the primary ones. It is especially characteristic that the cholesterol deposits disappear when the serum cholesterol value is reduced through a change for the better in the responsible disease, or when the patient is put on a

Table II.

Cause of hypercholesterolemia. The diseases which frequently are causing secondary xanthomatosis.

1. Increased fat resorption: Alimentary lipemia
2. Transport lipemia with increased requirement: Pregnancy
3. Transport lipemia owing to defective carbohydrate metabolism:
 - a) *Diabetes mellitus*
 - b) *van Gierke's disease*
 - c) *Acetonemic vomitings*
 - d) *Phosphorous poisoning (?)*
 - e) *Fasting*
4. Defective removal of fat:
 - a) *Myxedema*
 - b) *Idiopathic familial hyperlipemia*
 - c) *Bile obstruction.*
5. Hypoproteinaemia:
 - a) *Nephrosis*
 - b) *Glomerulonephritis*
 - c) *Cachexia*
6. Hormonal:
 - a) *Diseases of the pancreas*
 - b) *Premenstrually*
 - c) *Castrates*
 - d) *Cushing's syndrome*
7. Lipidoses:
 - a) *Primary xanthomatosis*
 - b) *Niemann-Pick's syndrome*

diet poor in cholesterol. Secondary xanthomatosis may accompany almost every form of hypercholesterolemia when this condition is of sufficient magnitude and has lasted long enough. The changes involved may therefore be encountered in a number of diseases where the serum cholesterol content is increased. These diseases are recorded in table II, where the most frequent causes of secondary xanthomatosis are pointed out.

The histological changes too are different from those accompanying primary xanthomatosis. Thus the foam cells are not so frequent, and extracellular cholesterol is more often encountered. The localization of the xanthomatous changes is also different. Thus eruptive, papulous xanthomata are found on the skin, and enlargement of the liver and spleen is frequently observed. As a combination it is often seen that a primary xanthomatosis becomes manifest, the cutaneous changes appearing when hypercholesterol develops for some other reason. Thus it is frequently observed that eyelid xanthelasmata first appear in connection with pregnancy (Frotscher). There is one respect, however, in which the secondary xanthomatosis resembles the primary one; it seems to make the patient more disposed to early arteriosclerosis.

The following two cases are presumably to be included in this category of secondary xanthomatosis:

Case No. 9. Woman aged 69. 8 to 9 years ago she developed an opacity in the right cornea, owing to a deposit of cholesterol crystals. At the same time sugar was found in the urine, and the blood sugar (fasting) was found to be 0.130 %. The patient moreover complained of some breathlessness. The serum cholesterol value was then 418 mg %. During a diet, which was suitable for diabetes and at the same time low in cholesterol, the serum cholesterol value dropped so that in 1937 it was 292 mg %. At the same time there was improvement of the sight. The patient never had angina pectoris, but during recent years attacks of intermittent claudication. The blood pressure was 170/100 when last measured.

Case No. 10. Man aged 61. In 1935 he came to the Eye Clinic of the Hospital because of large white spots in both corneas. The spots were due to deposits of cholesterol. When investigating his diet it was found that he, who was a cheesemonger, was very fond of all kinds of milk products especially cheese. His diet was therefore adjusted so that it became poor in cholesterol; moreover, he was given thyroid tablets. The cornea spots disappeared by this treatment so that the patient, who previously had been just able to distinguish light impressions and therefore had been helpless, now could find his way so that he could walk alone in the streets;

later he was able to read the headlines in the newspapers. In 1937 the serum cholesterol value was found to be 310 mg %. Since 1939 there had been a small amount of sugar in the urine, and since 1942 a mild angina pectoris.

Schüller-Christian's Disease.

As representative of the 3rd group of diseases, which rather incorrectly are grouped with xanthomatoses, we shall here mention 3 cases.

Case No. 11. Girl aged 12. No similar case can be found in the family. When 5 years of age she developed left-sided exophthalmus. She was therefore admitted to the Eye Clinic of the Hospital in 1937. An operation disclosed a thickening of the roof of the orbit; it was removed with a chisel, but the improvement was only slight. Hence she was again admitted in 1941, this time to the Otological Clinic. Inasmuch as the exophthalmus was unchanged she was again operated upon and there was removed some abnormal bone tissue from the roof of the orbit. Microscopy showed changes as in the Schüller-Christian disease, with typical foam cells.

Physical examination showed nothing abnormal beyond exophthalmus. More particularly, there were found no xanthomata. The serum cholesterol value was 243 mg %. X-ray examination of the cranium and the bones of the extremities showed nothing abnormal. The diuresis was 500 ml in 24 hours.

Case No. 12. Girl aged 9. Except for the usual childrens' diseases she had been of good health. 1— $\frac{1}{2}$ months before examination there appeared, without preceeding lesion, a swelling of the forehead with a rise in temperature that lasted for a couple of days. Since then the swelling increased. Otherwise no complaints.

Physical examination showed the skull somewhat asymmetrical, with a protuberance of the right frontal bone, covered with natural skin. No xanthomes were observed. X-ray examination of the cranium showed a 2×3 cm large defect which looked like that of Schüller-Christian's disease. Serum cholesterol value 124 mg %.

The patient was then admitted to the Neurosurgical Clinic of the Hospital where the tumor was removed. Microscopy showed changes which were typical of the Schüller-Christian disease, though it was impossible to find any foam cells in the preparation.

Case No. 14. Woman aged 20. She had suffered for 1— $\frac{1}{2}$ year from a skin disease that started on the forehead, but later spread to the back, the neck and the extremities. Otherwise no complaints. She received various treatments at the Skin Clinic of the Hospital, but with no particular results.

Physical examination showed skin disease localized to the fingers, the dorsal side of the forearm, the face, neck and back — appearing as nodules,

yellowish and up to the size of a pea. Upon microscopy they showed xanthomatosis. No other abnormalities were observed. Serum cholesterol value 142 mg %.

These three cases represent monosymptomatic manifestations of what is called the Schüller-Christian disease. In Nos. 11 and 12 we find the characteristic osseous granulation tumors, in the first case accompanied by exophthalmus. None of the patients showed diabetes insipidus or bone changes elsewhere. The 3rd case showed the characteristic skin disease, without osseous changes. In addition to these manifestations the literature speaks of a disease of the lungs in the form of diffuse fibrosis, and a disease of the lymphatic glands, especially found in the retroperitoneal glands.

As mentioned before, it is hardly possible now to classify this disease with the xanthomatoses. For one thing, the characteristic tissue with foam cells is not found in all cases — see for example case No. 12. According to Engellbreth-Holm, Teilum and Erna Christensen the characteristic tissue is a granulation tissue which frequently may contain typical foam cells, but also may contain eosinophilic cells with transition to eosinophilic granuloma. Thus it seems most natural to consider the cholesterol deposit from the same point of view as that taken with regard to the cholesterol that may be found in malignant tumors, like mammary cancers or those occurring in malignant lymphogranulomatosis. As a matter of fact, patients of this kind have in general a normal serum cholesterol value, as in the case of the three patients described by the author. There have been cases published, however, where the serum cholesterol value was increased, but it is not known how much significance should be attributed to these observations. The rare cases described as transitional stages between Schüller-Christian's disease and xanthomatosis must presumably be considered chance coincidences.

It will be understood that the knowledge of the xanthomatoses is of no small practical importance, inasmuch as we here have a nosologically well defined form of arteriosclerosis where there may be a possibility for prophylactic treatment. Everything considered, the interest in the xanthomatosis as a relatively rare anomaly of the metabolism should be replaced by a consideration of the far more important problem of its significance to the early arteriosclerotic heart diseases and the early death from heart failure.

Summary.

On the basis of 8 cases the author reviews the primary xanthomatosis with special regard to the heart complications. The heredity of the disease is emphasized, and 4 genealogical tables are recorded which indicate that the disease is a dominant factor. Its significance to an early arteriosclerosis in aorta and the coronary vessels is investigated. Both among the patients and in their families there were found several instances of early death by heart failure, which in most cases was preceded by angina pectoris. In contrast, the secondary xanthomatosis shows entirely different localizations. It is probable, however, that this kind of cholesterolemia entails an increased risk of early arteriosclerosis. The Shüller-Christian disease, which generally has been classified with the xanthomatoses, must, according to recent investigations, be put in an entirely different class. The author cites three cases, one of which is significant by not showing any xanthomatous cells upon microscopy, thus confirming this point of view.

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The Frequency of reduced Lacrymal Secretion in Xerostomia.¹

Studies in Xerostomia V.

By

MOGENS FABER.

(Submitted for publication May 3, 1944).

Investigations on Mikulicz' syndrome have shown that the responsible disease in most instances affects both salivary and lacrymal glands. There was nothing especially strange in this as long as the disease was considered a result of a generalized affection. There is much, however, to indicate that a substantial number of patients with this disease suffer from a chronic canalicular inflammation of both the salivary and the lacrymal glands, and that this inflammation is due to reduced secretion. By analysing a considerable number of cases of xerostomia the author demonstrated how the patients show a tendency to inflammatory conditions in the salivary glands, both acute and chronic conditions being involved. It should therefore seem reasonable that the affection of the lacrymal glands in the case of Mikulicz' syndrome at least in some instances have the same origin.

In his doctoral thesis dealing with keratoconjunctivitis sicca Sjögren emphasizes that in a considerable number of his patients he found a reduced salivary secretion in addition to the decreased lacrymal secretion. In a previous paper the present author, having

¹ Aided by a grant from the P. Carl Petersen Foundation.

a smaller material at his disposal, has shown how reduced lacrymal secretion frequently occurs simultaneously with xerostomia. In order to find out how close this association is the author has made parallel investigations of the salivary secretion and the lacrymal secretion in 87 patients. Since these patients are included in an investigation of xerostomia, this anomaly will be found most frequently, only a few being examined owing to a known reduction of lacrymal secretion. Most of the patients, however, are examined as supposedly normal in this respect.

The lacrymal secretion is measured according to the method of Schirmer. A 5 mm wide piece of filter paper is, with a slight bend, placed laterally in the conjunctival sac. Measurement is then made of the height to which the paper has become moistened in the course of 5 minutes. Sjogren reports the lowest normal value as 15 mm in 5 minutes. Schirmer's other test, where the secretion is measured after indirect stimulation, has not been employed; this test may be classified with that involving the measurement of the salivary secretion after stimulation with pilocarpine, a test which has been found to show a reduction only in the case of pronounced, frequently histologically demonstrable changes in the salivary glands. It was not the intention to confine the investigation to cases as severe as that.

The salivary secretion is measured according to M. Faber (1943). The saliva is collected quantitatively by means of suction through a bifurcated tube in 3 periods of 10 minutes each. The largest amount of saliva collected during the last 2 periods expresses the magnitude of the secretion. The amount is expressed in ml per minute. Normal values are 0.3—0.6 ml per minute, but for a definite reduction the value must fall below 0.2 ml per minute.

The results (see fig. 1) show a surprisingly good agreement between the reduction of the salivary secretion and that of the lacrymal secretion. A reduction of the secretion from both sets of glands was observed in 27 cases, while 25 cases showed a reduction which affected only one of the systems. In 46 additional instances the secretion was found to be normal in the case of both sets of glands, and among these 46 there were some with ample secretion.

The cause of the observed simultaneous reduction of the secretion of the two gland systems is as yet unknown. The table records

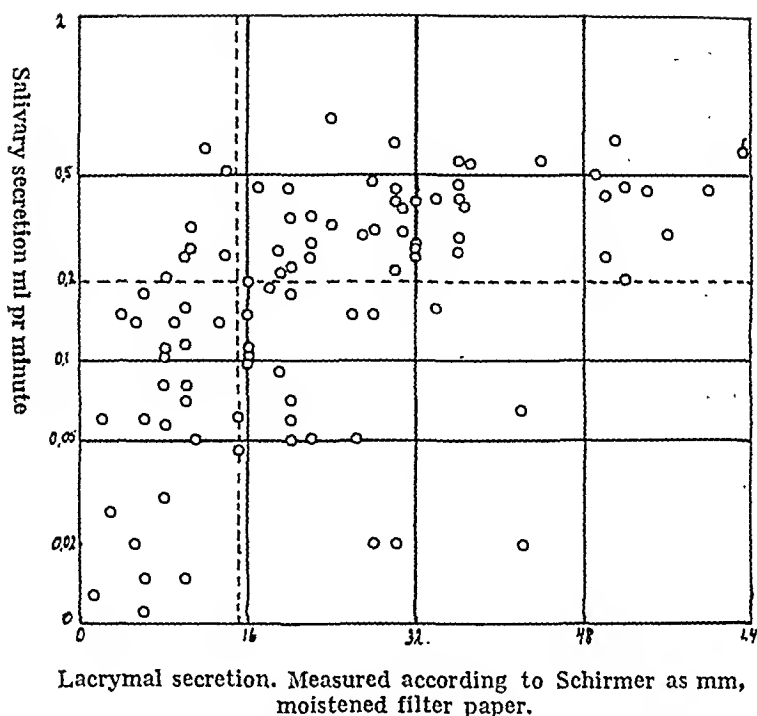


Fig. 1. The relationship between salivary secretion and lacrymal secretion. The dotted line indicates the lower border of the normal secretion.

the supposed causes, in so far as they may be judged from the disease of the patient, the diseases being stated which, according to Faber, are frequent causes of xerostomia. It will be seen that the material does not contain any instances of Miculicz' syndrome, or chronic sialoid or lacrymal adenitis, since these diseases often may be localized to one gland system only, and then frequently be due to changes which have nothing to do with the problem under consideration. That the material consists predominantly of women is due to the circumstance that women are in majority among the xerostomia patients as well as in most of the groups of diseases investigated, so that they are chosen to give a larger number of patients with reduced secretion. It will be seen that a simultaneous reduction of the two secretions can be found both in the mixed group and in the group of picked diseases. That the connection is so little pronounced in the case of pernicious anemia and diabetes mellitus is probably due to the circumstance that so few patients with these diseases have been included. The mixed group is of

Table 1.

Lacrymal secretion Salivary secretion	Normal		Low		Normal		Low	
	Normal		Normal		Low		Low	
	M.	F.	M.	F.	M.	F.	M.	F.
Diabetes mellitus	3	1	0	1	0	2	0	3
Pernicious anemia	1	0	0	0	2	2	0	1
Sideropenic anemia	0	3	0	1	0	4	1	5
Myxoedema	0	4	0	0	0	2	0	1
Sprue.....	0	0	0	0	0	1	0	0
Others	11	23	1	4	1	4	1	15
Summa	15	31	1	6	3	15	2	25

course very heterogenous, but seems to show better correlation than the other groups, especially in the case of the women. The most essential feature in common for these female patients is their age — all of them, with one exception, having passed the climacteric. But it is wrong to associate the complaint with senility, only 6 of the 15 women being more than 60 years of age.

The material does not permit us to conclude what is the cause of this connection between the reduction of the salivary and the lacrymal secretions. A few facts may be pointed out: Thus it appears that the innervation of the salivary glands is intimately connected with that of the lacrymal glands, the parasympathic fibres originating in the same nuclei and running parallel towards the periphery through the same nerves, so that a lesion of nerve fibres leading to one gland easily may be accompanied by a damaging of the nerves of the other gland. It seems less probable, however, that a cerebral disease should be responsible, although this possibility cannot be excluded. A fact that tells against it is that patients with reduced salivary and lacrymal secretions in most instances as a parallel symptom also show a reduced stomach secretion, an achylia gastrica, and in some cases a reduced vaginal secretion.

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Protein and Amylase in the Saliva from Normal Individuals and from Patients with Xerostomia.¹

Studies in Xerostomia VI.

By

MOGENS FABER.

(Submitted for publication May 3, 1944).

A number of earlier papers have dealt with the occurrence of a reduced salivary secretion and the conditions under which this phenomenon appears. The findings are in the main in agreement with those described by Fabian in his monograph, although some deviations have been found. Thus the present author has observed the reduced salivary secretion most often in connection with achylia gastrica, though this is not always the case. The reduced salivary secretion in pernicious anemia is e.g. found to be most frequent in the anemic periods, and in most cases the secretion will again become normal during the specific treatment of the anemia. The papers by the author have emphasized that, with our present knowledge, it is impossible to furnish a more detailed analysis of the pathogeny of such a reduction of the salivary secretion. It is only possible in the cases where a definite local affection of the salivary glands can be demonstrated, most frequently in the form a chronic inflammation. In the other cases it is not known whether the reduction of secretion is dependent on changes in the gland itself or whether the origin is central.

¹ Aided by a grant from the P. Carl Petersen Foundation.

It seemed possible that an investigation of the composition of the saliva might yield some information. Hence, in a number of instances analyses have been made of the contents of amylase and protein in the saliva, normal individuals as well as patients with reduced secretion being included in the investigation.

Technique. The saliva is collected by continuous suction through a bifurcated tube placed under the tongue. The saliva is first collected during 3 periods of 10 minutes each, so that the basal secretion may be measured. The individual is then given a subcutaneous injection of 2.5 mg of pilocarpine and the saliva is collected for yet another 2 periods of 15 minutes each. The basal secretion is recorded as the highest secretion during one of the two last preliminary periods, and is expressed in ml per minute. The secretion after injection of pilocarpine is similarly expressed, as the secretion per minute in the largest portion. As a rule the collection is carried out while the patient is fasting, or at any rate several hours after his last meal. In the protein determinations the first portion is rejected in order to eliminate any possible error due to detritus protein, while all portions are used for the amylase determinations.

With a few modifications the technique which Nørby has developed for blood is used in the determination of amylase. As long as the cleavage of starch caused by the amylase does not exceed 40 % the reaction will be monomolecular and the reaction constant will be proportional to the amount of amylase. The latter is expressed by the reaction constant multiplied by the dilution, which in most experiments has been 1:500. The time of experiment has been 30 minutes, and the temperature 37° C.

The protein determinations are made on fresh saliva, calculated as the difference between the total nitrogen and the nitrogen content after precipitation of the protein with tannic acid, as it is found extremely difficult to collect the protein quantitatively after the precipitation. Nitrogen is determined in the apparatus of Parnas and Wagner.

As regards *amylase* the experimental results are recorded in table 1. A total of 28 persons have been examined. The 7 samples of saliva from normals show an average amylase activity of $2.195 \pm$

Table 1.

The amylase content of saliva at varying rates of secretion before and after pilocarpine.

No	Secretion at rest			Secretion after pilocarpine			Serum amylase
	ml saliva pr minute	Amylase		Ml saliva pr minute	Amylase		
		units pr ml saliva	units pr minute		units pr ml saliva	units pr minute	
Normal							
1	0.52	0.938	0.488	1.88	2.435	4.58	0.00416 0.00392
2	0.51	1.448	0.743	1.70	2.834	4.82	
3	0.37	2.500	0.933	1.62	3.022	4.90	
4	0.47	2.892	1.368	1.73	2.487	4.30	
5	0.48	1.945	0.938	2.33	2.625	6.11	
6	0.36	2.892	1.033	1.67	2.950	4.93	
7	0.33	2.750	0.908	1.27	3.232	4.11	
Patients with normal secretion							
8	0.62	3.050	1.891	1.00	2.570	2.57	0.00594
9	0.28	3.445	0.965	0.80	3.215	2.58	0.00878
10	0.67	2.384	1.597	1.82	2.006	5.29	0.00248
11	0.62	2.051	1.272	1.00	2.512	2.51	0.00538
12	1.33	1.543	2.052	1.20	1.863	2.23	
13	0.43	1.425	0.618	1.50	1.962	2.94	
14	1.21	1.628	1.970	2.40	2.693	6.46	
15	0.48	0.648	0.311	1.70	2.168	3.69	
16	0.29	3.082	0.894				
17	0.23	3.142	0.723	1.07	3.323	3.56	
Patients with xerostomia							
18	0.07	0.625	0.044	0.15	0.603	0.09	0.01034
19	0.14	0.367	0.051	0.77	2.785	2.14	0.00686
20	0.13	1.911	0.248	0.97	2.862	2.78	
21	0.05	0.207	0.010	0.87	2.780	2.42	
22	0.07	0.764	0.053	0.63	3.050	1.92	
23	0.14	2.892	0.405	0.70	2.568	1.80	
24	0.07	3.415	0.239	1.50	3.248	4.87	
25	0.01	0.470	0.005	0.08	0.247	0.02	0.00106
26	0.01	3.052	0.031	0.12	3.568	0.43	0.00290
27	0.13	2.907	0.378				0.00332
28	0.17	1.812	0.308	0.97	2.500	2.42	

Mg Protein pr ml saliva

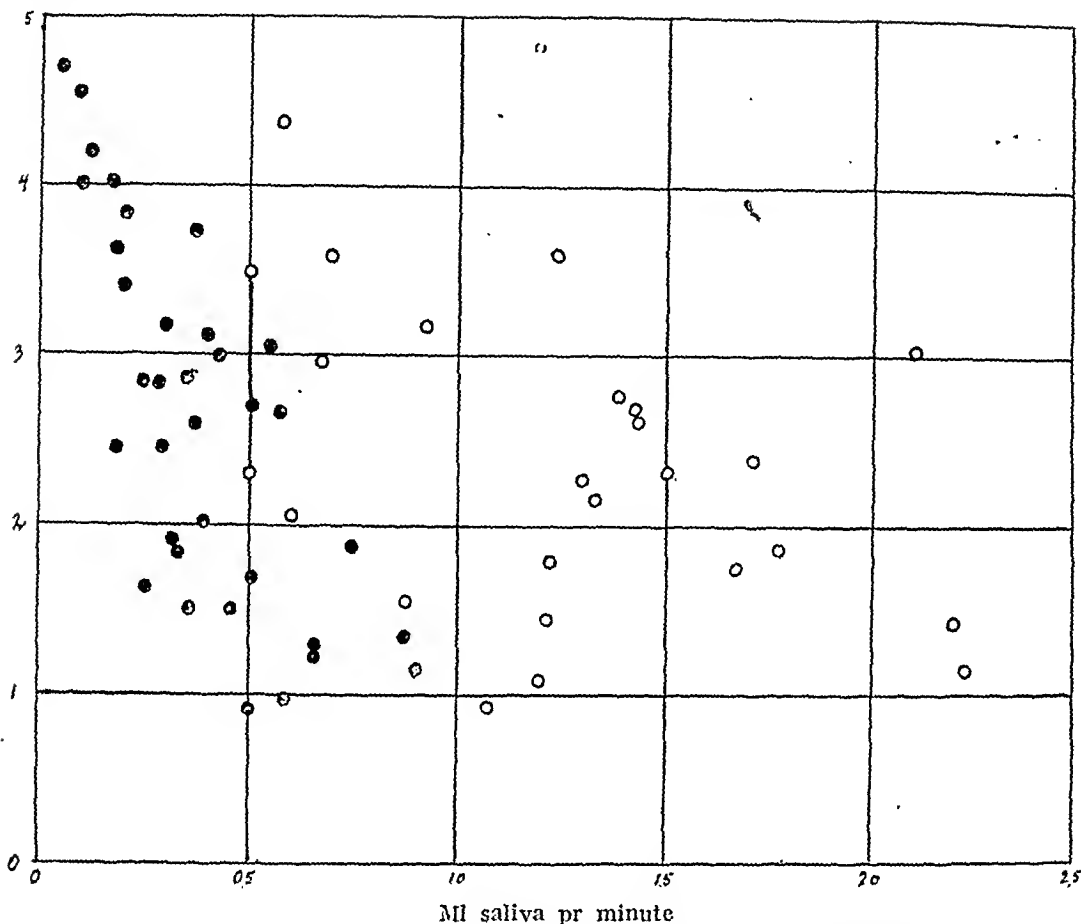


Fig. 1. Protein content of saliva before • and after ° pilocarpine injection

0.359 units. The 10 samples from patients with normal or but slightly reduced salivary secretion show an average amylase activity of 2.240 ± 0.376 units. 11 patients with a definitely, most often very considerably reduced secretion give the average of 1.674 ± 0.405 units. The difference of 0.548 units which is here found between patients with normal secretion and patients with reduced secretion is not sure, however, since the mean error of the difference between the mean values is 0.424. More distinct and significant is, however, the reduction of the amount of amylase secreted per minute in the patients with reduced salivary secretion. The injection of pilocarpine is followed by an increase of the

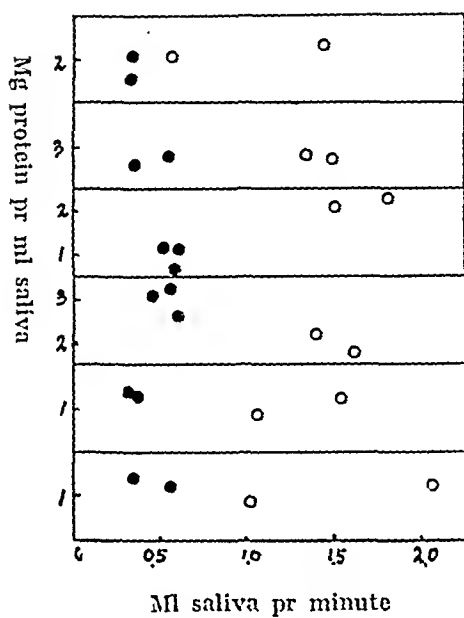


Fig. 2. Protein content of saliva before • and after ○ pilocarpine injection in 6 normal cases

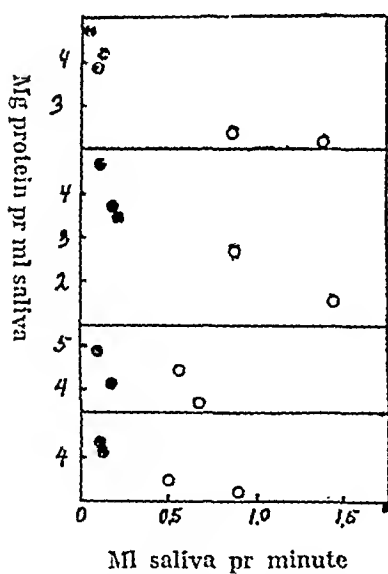


Fig. 3. Protein content of saliva before • and after ○ pilocarpine injection in 4 cases of xerostomia.

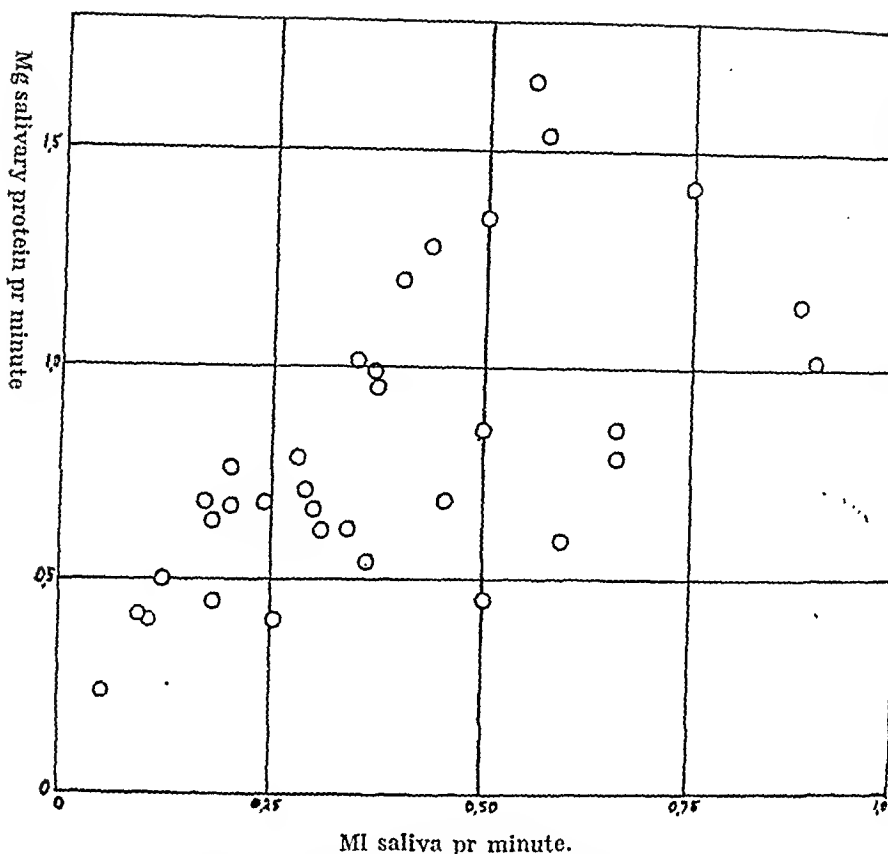


Fig. 4. The amount of protein secreted pr minute at varying rates of salivary secretion.

amylase activity of the saliva in all three groups examined, to values of 2.798, 2.468 and 2.321 respectively, so that the rise is the highest in the group with the lowest basal secretion. The amount of amylase secreted per minute, however, show a much smaller rise in the last mentioned group.

A few cases also include a determination of the amylase in serum, but it has been impossible to demonstrate any correlation between the amount of serum amylase measured and the simultaneous amylase content of the saliva.

In the case of *protein* the results of 35 analyses are recorded in fig. 1. It will be seen that the protein content of the basal saliva shows a definite dependence on the rate of secretion, the data

disclosing that the samples which are secreted at the lowest rate contain most protein. The average protein content of the samples that are secreted at a reduced rate is 3.8 mg per ml, while the samples secreted at normal rate show an average of 2.06 mg per ml. The injection of pilocarpine is, as a rule, followed by a fall in the protein content. This, however, does not apply to the samples from the 6 normals, as seen in fig. 2. But there is always a fall in the case of xerostomia patients, see fig. 3. The rise in the protein content of the saliva which is secreted in reduced amount is not large enough to compensate for the decrease in the amount of saliva, so that these patients also in the case of the protein show a reduction of the total amount secreted per minute, see fig. 4.

Discussion. Patients with reduced salivary secretion thus show a larger protein content of the saliva than normal individuals, both pr ml saliva and pr minute. The amylase content seems to be reduced, though the data are uncertain when measured pr ml saliva, but appear satisfactory when measured pr minute. These findings agree reasonably well with the statements in the literature concerning the normal secretion. In an investigation of normals Bramkamp thus finds an increase in the protein content of the secretion from the parotid gland at increasing rate of secretion, but in the mixed saliva from all glands he finds no variation. Experiments by Carlsen and Crittenden show for increasing secretion the largest amylase content in the saliva which is secreted at the highest rate. Delhougne finds a rise after mastication and histamine injection, but a fall after stimulation with pilocarpine.

Very few investigations deal with the conditions in the case of pathologically reduced secretion. Charles and Dalmas-Monsalet find a decrease of the amylase content in patients with reduced salivary secretion. Similar results are obtained by Meyer, Golden, Steiner and Neeheles in old age where the salivary secretion is lower than in the young. The more scanty saliva of infants likewise shows a lower amylase content (Mayer). Fabian, however, finds no correlation between the rate of secretion and the amylase content. The present author has been unable to obtain information regarding earlier investigations on the protein content in the case of reduced salivary secretion.

The material here presented, dealing with patients with xerostomia, includes both patients with a definite disease of the salivary glands (epidemic parotitis (case nr 18), chronic sialadenitis (case no 25) and congenital aplasia of the salivary glands, especially parotis (case no 26), all studied with regard to amylase content) and patients where the xerostomia is due to other causes. The first mentioned patients do not show any difference from the other xerostomia patients in so far as the substances investigated are concerned. It is impossible, however, from this circumstance to draw any definite conclusion regarding the mechanism of the reduction of the salivary secretion, although its origin at least in the three cases mentioned would seem to be peripheral. Other facts fail to support the idea. Even though the reduction of the amylase concentration at low salivary secretion is not sure in the present investigation, it seems rather probable, especially when measured *pr minute*. A reduction in amylase and a rise in protein would agree with the idea that the reduction of secretion first of all has affected those parts of the salivary glands which produce a serous secretion. This secretion, which first of all has its origin in the parotid gland, will be rich in amylase, while the largest addition of protein to the saliva would come from the mucous glands. This is in agreement with the clinical observation that it more frequently is the parotid gland which is affected in chronic sialadenitis. What is said here rather supports the theory of a central cause of the xerostomia.

Summary.

The amylase and total protein content of saliva secreted at normal and reduced rates is compared. The amylase content of the saliva in patients with xerostomia is found slightly reduced *pr ml* saliva, but when measured per minute the reduction is more definite. The protein content is found higher the lower the rate of secretion. These findings suggests that the reduction of the secretion in xerostomia first and strongest will affect the serous, especially the parotidic secretion. The mechanism of the reduction is not evident from these findings.

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Methylscopolamine nitrate,¹ a new vegetative antispasmodic,

and

A review of the investigations on the effect of the atropine group on nonstriated gastro-intestinal muscle.

By

EBBE NYMAN.

(Submitted for publication May 21, 1944).

The effect produced by the alkaloids of the atropine group on the tone and motor functions of the abdominal alimentary organs has been the subject of much discussion, not the least interest having centred around their value in the treatment of pain arising from ulcers. Despite the fact that very variable results have been obtained both from animal experiments and in clinical medicine, these substances have continued to be used by clinicians for more than half a century as vegetative antispasmodics. As regards the ulcerous conditions, some observers have paid more attention to the secretion inhibiting action of these drugs, while others have concentrated more on the aspect of the spasmolytic effect they exercise on the vegetative system. Our present view of the matter has perhaps been summed up most satisfactorily by Kalk and Siebert (1927) in the following manner: »Das Problem des Magenschmerzens und seiner Beeinflussung durch Atropin ist vielmehr ein Problem des Tonus und der Motilität als der Sekretion».

¹ Manufactured and sold by A. B. Pharmacia, Stockholm, under the name of »Skopyl».

von Bezold and Bloebaum (1867) were among the first to study the action of atropine on the intestines. Working with laboratory animals, they found that large doses gradually caused paralysis of the normal intestinal functions. Keuchel (1868), who also experimented with animals, noted that small doses of atropine injected intravenously stimulated the spontaneous mechanism of the intestines. Hagen (1890) later made the same observation. In 1886, Schütz observed that contractions produced by muscarine or pilocarpine in the stomach of the dog were inhibited by small doses of atropine, and that an increase in the dose caused a considerable decrease of tone, and dilatation of the stomach *in situ*. The motor mechanism was hindered also when the dog's stomach was isolated.

Bayliss and Starling (1899), on the other hand, found that atropine could not prevent the effect produced by vagal stimulation in the dog's intestine.

The method introduced by Magnus (1904), by which graphic records were made of the contractions in isolated, surviving pieces of intestine suspended in a physiologic saline solution through which a stream of oxygen was passed, opened up new possibilities for studying each of the various motor functions separately. By means of this technique, Magnus (1905) was able to establish that the initial excitation sometimes observed in connection with atropinization of the intestines is brought about solely by an impulse from the autonomic nervous system (Auerbach's plexus). Pieces of intestine painstakingly freed from all connection with the plexus did not display this augmentation in the contraction rate; they only became paralyzed as a result of the administration of atropine. Magnus stated his views on the effect of atropine on the intestines in the following summarized form.

1. In pieces of intestine not freed from plexus fibres, an initial augmentor effect occurs even with 0.025—0.075 per cent atropine in Ringer's solution, especially if the intestine has previously displayed a decrease of motility.

2. With the same strength of atropine, the contractions gradually become regulated, particularly in longitudinal fibres to which the plexus is attached, resulting in a constant tone and regular pendulum movements.

3. Paralysis of the intestine occurs only when strengths of over 0.05 per cent atropine are applied. In specimens freed from plexus

fibres, paralysis was first observed with strengths around 0.2 per cent.

Thus, the conditions described by Magnus can be said to be rather complicated. For practical purposes, Magnus (1907) came to the following conclusion: »Für die therapeutische Beurteilung des Atropins kommt hier nur die Wirkung der kleinsten Dosen in Betracht, also erstens die Erregung der Darmbewegung und zweitens ihre Regularisierung». A similar point of view was expressed by Kress (1905).

In a joint publication, Langley and Magnus (1905—1906) demonstrated that a 1 per cent atropine solution applied locally to the small intestine of the cat usually produces strong contractions confined to a small area, and of short duration and reproducibility. In the descending colon of the rabbit, when the records were made by the balloon method with the intestine *in situ*, the tone was increased and the mechanical movements became regulated.

Unger (1907) obtained in the main the same results as Magnus, but he mentioned having also observed an inhibitory effect when much lower strengths of atropine were used. In experiments on the small intestine, using the Magnus technique, Unger noted that concentrations of between 0.000005 and 0.0025 per cent atropine, or between 0.05 and 25 mg of atropine per litre of normal saline solution, caused a relative degree of inhibition together with decrease of tone and levelling of the variations. It was not until he raised the strength to 0.006—0.016 per cent that he was able to obtain the augmentor effect previously demonstrated by Magnus. Magnus (1908) questioned the correctness of Unger's findings, and suggested that his results must be due to experimental errors, the exact nature of which are not stated, however. Van Lidth de Jeude (1916, 1918), in a comprehensive publication, reported observations supporting the results obtained by Unger.

According to Hirz (1913), no stimulatory effect occurs when atropine is applied to the rabbit's intestine. In the cat, he obtained sporadic evidence of augmentation of tone and of increased intestinal movement. Trendelenburg (1917) attacked the problem by another method which aimed at recording the intestinal contractions in isolated pieces of guinea-pig intestine. In order to supply an excitatory stimulus he stretched the suspended piece of intes-

tine, which was filled with, and immersed in Tyrode's solution. By means of this technique Trendelenburg was able to show that in the small intestine of the guinea-pig the peristalsis is inhibited by atropine at any strength. The rabbit's intestine, on the other hand, did not give such unequivocal results. In this connection Trendelenburg pointed out the similarity between the reaction of the guinea-pig's intestine and that occurring in Man. At an earlier date, in fact, Katsch (1914) had demonstrated, on the evidence of roentgenographic studies using contrast solutions in human beings, that atropine, in doses therapeutically usable, causes broadening of the outline of the small intestine, smoothing of Kerkring's folds, and retardation of the passage of the contrast. Yet, in spite of this, there had been no signs whatsoever of initial excitation. Even before this, also, Katsch (1913) had found, by examining the rabbit's intestine *in situ* through an abdominal fenestra, that not even with this experimental method did atropine produce any augmentation in the motor mechanism; in every experiment its action was solely inhibitory. Katsch's results may be briefly summarized as follows:

Atropine causes in man:

1. Diminution of the intestinal movements, especially in the colon.
2. Decrease of tone of varying degrees, this being reflected, for instance, in increased colonic width, increased width of the small intestine and obliteration of Kerkring's folds, flaccidity of the colonic sacculations, lengthening or even folding of the transverse colon, and opening of the ileocecal valve.
3. Prolongation of the passage through the small intestine, but acceleration through the colon, at least when the muscles are spastic and when there is a slow spontaneous evacuation.

With a view to attempting to account for the variable results regarding the influence of atropine on the intestines, Liljestrand (1919) took up the question of the varying content of atropine and and l-hyoscyamine in the atropine preparations used in this type of experiment. He did not succeed in proving that this aspect was of any significance, since both atropine and l-hyoscyamine exercised the same effect both qualitatively and quantitatively on the intestine of the rabbit, the cat, and the guinea-pig, and on the rabbit's and the guinea-pig's intestine the same quantitative effect

was obtained. Nor could Liljestrand confirm the observation made by Cushny (1904), that l-hyoseyamine was twice as active as atropine on unstripped muscle also. In Liljestrand's experiments also, an excitatory effect of atropine on the intestine was observed, especially if the intensity of the spontaneous movements had previously been lowered.

The experiences from these various types of experiments on laboratory animals form the background of the present methods of applying atropine in clinical practice, not only for the regulation of the motor functions of the intestines, but for the stomach also. The absence of studies on the ventricular movements in animals is very striking. In all probability the reason for this is that investigations of this nature present certain difficulties, in that it has not been possible to isolate from the stomach functional units equivalent to those taken from the intestine.

Among the more recent investigations on the action of atropine on the intestines may be mentioned those undertaken by Straub and Muñoz Fernandez (1933). These observers did not consider they could obtain reliable results from isolated pieces of intestine, and their method was therefore to insert manometers into the small and large intestines of the guinea-pig, *in situ*. With this technique they found, to state it briefly, that neither atropine, l-hyoseyamine, nor scopolamine, in therapeutically usable doses (10 γ per Kg of body weight), produced an effect on the peristaltic movements in any segment of the intestine. On the other hand, even the mentioned dose caused a considerable general lowering of tone. In this respect, atropine and l-hyoseyamine mainly affected the small intestine, and scopolamine the large intestine.

Of the large number of clinical investigations and reports on the action of atropine on the gastro-intestinal tract, only a few can be mentioned here.

Rieder (1906) reported good results in the treatment of the so-called hourglass stomach. von Bergmann (1913) took up the question in connection with his spastic ulcer theory. He considered atropine to be clinically useful as a tone-reducing agent for ulcers, as well as for other conditions, an opinion which has since been held almost without exception by most clinicians.

Zuntz and Tysebaert (1916) maintained that, judging from their observations on clinical material, to produce an effect on both

tone and peristalsis different amounts of atropine were required. Thus, a lowering of tone, according to them, was easier to produce than inhibition of the peristalsis. Katsch (1914) had shown, in the roentgenographic investigation already mentioned, that atropine delays the emptying of the stomach's contents, and this observation has since been confirmed by many investigators, among others Klee (1920), and Lockwood and Chamberlain (1922).

Laseh (1922) also obtained in a clinical series, in connection with roentgen examinations of the stomach, the same initial stimulation due to atropine as that noted by earlier observers in animal studies. According to his findings, there was augmentation of the peristaltic movements in the stomach 15—20 minutes after the injection of atropine, before inhibition and atony occurred. In this series also, there was delayed evacuation, despite the fact that in most instances the pylorus was so wide open that the examiner could with ease press out the contrast solution into the duodenum. Much difference of opinion has been expressed regarding the behaviour of the pylorus after the administration of atropine. In contrast with the features noted by Laseh (1922), Klee (1920) found that the deferred emptying of an atropinized stomach was not due to atony, but that the explanation was rather to be sought in an increase of tone in the pylorus. Ötvös (1921, 1922) drew the same conclusions from roentgenographic evidence obtained from human beings. In healthy subjects, not even 1—1½ mg of atropine, administered by injection, produced any definite effect on the peristaltic waves and the tone of the stomach; in patients with an ulcerated stomach, on the other hand, the emptying time was prolonged, a feature which was ascribed by Ötvös to an excitatory effect of the atropine due to heightened irritability of the pylorus (Auerbach's plexus) brought about by the ulcerative process. In healthy persons the lower degree of irritability in the pylorus was in his opinion counteracted by the presence of a motor mechanism of equal strength in the fundus musculature, capable of overcoming the resistance of the pylorus. This explanation, however, seems slightly complicated, to say the least of it. Klee (1920) thought a preponderance of the sympathetic tone in the pylorus might be present under the influence of atropine, but at the same time he endeavoured to illustrate the probable unimportance of this factor by demonstrating that although the pylorus is open after sectioning

of the splanchnic nerves the emptying time is nevertheless prolonged.

In comparison with the experiments pointing to the likelihood that pyloric spasm is the effect produced by atropine, we may place the empirical experiences gained from the treatment of infantile pylorospasm with atropine derivatives, the most striking, and up to the present the most efficacious of which has been methyl-atropine nitrate (methatropine). In the case of the latter, however, it has been a matter of considerably larger doses than those generally used with the other derivatives (Svensgaard, 1935).

There still remains established, however, the delaying action of atropine on the initial emptying of the stomach due, from what can be judged, to both lowering of tone and inhibition of the peristalsis. This effect has of recent years been confirmed repeatedly by different authors, among others by Kalk and Siebert (1927), by Herrin (1936), and by Nyman (1942).

In this connection, however, it should be stressed that, according to quite a number of publications, mostly from earlier years, atropine in therapeutic doses has no effect on the stomachal peristaltic movements in man. To this category belong the papers of Crohn (1918) and of Bastedo (1920).

In 1942, the author of the present paper showed that methyl-atropine nitrate has a much stronger peripheral, anticholinergic effect on a number of human functions than atropine sulphate. The likelihood was then also suggested that scopolamine compounds derived in the same way, that is, derivatives with methylated pentavalent nitrogen, might also possess properties of therapeutic value. A few preliminary observations were also reported in the same publication (1 c, p. 121). Since then, the preparation of methylated scopolamine derivatives has been continued, on the suggestion of the writer, and a number of investigations on their use have been carried out. Up to the present, the results of studies of their action on the salivary secretion, the pupil, and the cardiac branches of the vagus, and on the central nervous system, all of these in human beings, have been reported, as well as an investigation on their toxicity in mice (Nyman, 1943). The object of the present communication is to describe firstly, the experiences gained with one of these compounds, viz. methylscopolamine nitrate, and secondly, its effect as a vegetative antispasmodic in isolated,

surviving pieces of small intestine from the guinea-pig. Finally, a few preliminary clinical results are also presented.

The writer's investigations.

1. *Experimental studies.*

For the tests on the strength of the anticholinergic (parasympathicolytic, spasmolytic) effect of methylscopolamine nitrate, pieces of small intestine from the guinea-pig were isolated in a specially prepared bath in the manner described by Magnus (1904). In the same experiments the effects of scopolamine hydrobromide, atropine sulphate, and methylatropine nitrate were compared with the methylscopolamine effect. For details of the technique the reader is referred to the paper by Tarras-Wahlberg (1936). A piece of the jejunum, 3—5 cm in length, taken from a freshly killed, medium-sized guinea-pig was suspended in a glass-container with a capacity of 30 ml. This was filled with Tyrode's solution to which glucose (0.5 per cent) had been added, and a stream of oxygen (with 5 per cent carbon dioxide) was passed through it. The container was kept immersed in a water bath at 38° C. A freshly prepared solution of acetylcholine was the agent used to stimulate the intestinal movements. After a regular rhythm of contraction had been obtained from one and the same acetylcholine dose (usually 0.5 γ) — this did not occur until after the piece of intestine had been «trained» a little, the strength of the contractions gradually increasing up to a certain level — the inhibiting substances were added in constant amounts. Three minutes after the last change of solution the anticholinergic substance, in solution, was pipetted into the glass-container. Exactly 30 seconds later, the same dose of acetylcholine as had been used before was added. The tracing then obtained constituted a direct measure of the relative strength of the inhibiting substance. After an experiment of this kind the piece of intestine showed gradually decreasing irritability over a period of 30—45 minutes. As four different substances were being tested on the same piece of intestine in these experiments it was not always easy to maintain, or to reproduce, a constant state of irritability in the piece of intestine during the 3—4 hours required for the experiment. It was by no means always possible to obtain irreproachable series of tests in which the intestine had had time,

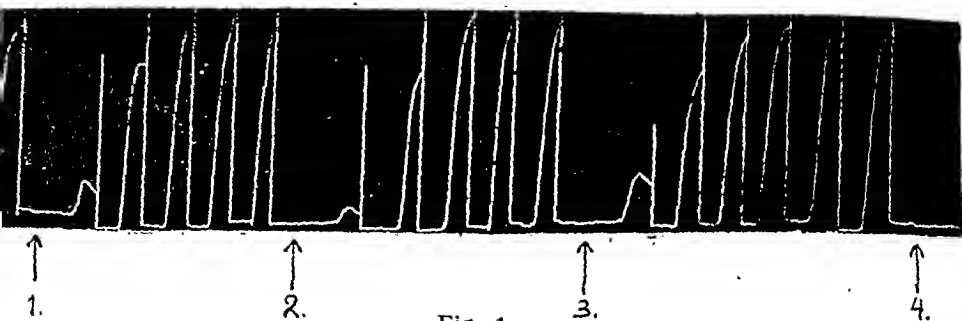


Fig. 1.

not only to recover from each dose of the inhibiting substances but also to regain a uniform capacity for responding to the standard dose of acetylcholine. In the material presented here, six out of the fifteen series give no cause for criticism. *No excitatory effect whatsoever, resulting from the different atropine and scopolamine derivatives was observed in these experiments.*

The course of an experiment carried out in the above-mentioned manner will be seen most clearly by glancing at the graphic records in figure 1.

The whole experiment illustrated by the curve represents a time of four hours. A time marker has not been shown because the curve also includes long periods of inactivity on the kymogram. The first tracings show the gradual approach of regular intestinal movements in response to the dose of 0.5 γ of acetylcholine. About five minutes elapsed between each addition of acetylcholine. At the first arrow 0.1 γ of atropine sulphate was added, and exactly 30 seconds later 0.5 γ of acetylcholine, a contraction then being obtained which was much weaker than that recorded after the addition of acetylcholine alone. After the intestine had been allowed to rest for about 30 minutes, during which time it was washed repeatedly, it rid itself of the effect of the atropine and regained its original sensitivity to acetylcholine. At the second arrow 0.1 γ of methylatropine nitrate, and after 30 seconds 0.5 γ of acetylcholine were added. The resulting contraction was even weaker than when the atropine was added at the first arrow. The same procedure was repeated at the third arrow, 0.1 γ of scopolamine hydrobromide being added this time, and at the fourth arrow the new agent, methylscopolamine nitrate, was used in the same dose. The latter drug almost totally inhibited the acetylcholine effect. In other

Table 1.

The relative strengths of certain atropine and scopolamine compounds as acetylcholine antagonists, measured in guinea-pig intestine.

Compound	Series no.:						Mean value
	3	7	8	11	14	15	
Atropine sulphate.....	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Methylatropine nitrate	2.0	—	1.6	—	2.5	2.0	2.0
Scopolamine hydrobromide	0.5	0.4	0.8	0.7	0.8	—	0.6
Methylscopolamine nitrate	5.0	6.4	7.4	5.9	4.2	4.4	5.5

experimental series the order in which the different derivatives were added was varied. The experiments were otherwise carried out under a standard set of conditions, the same for all tests. Fresh solutions of both acetylcholine and inhibiting substances were prepared for each experiment. The results are shown in tabulated form in table 1. The method of estimation was to measure the height of the individual contractions to within half a millimetre from the base and to calculate their height in per cent of the regular standard contractions occurring after the dose of acetylcholine, when there was no inhibiting effect. As already mentioned, no appreciable margin of variation was allowed in the standard contractions ($< 10\%$).

Thus, if the relative antispasmodic effect of atropine sulphate on guinea-pig intestine be made equal to 1, these experiments prove that methylatropine nitrate (methatropine) is twice as active. Further, that scopolamine hydrobromide is much weaker than atropine sulphate, and that the new agent, methylscopolamine nitrate, possesses a striking degree of activity in the connection treated corresponding to between five and six times the activity of atropine sulphate.

As regards the other properties of methylscopolamine nitrate, the reader is referred to the writer's previous publication on the subject (1943). For the sake of clarity, a tabulated review of the properties of the substance, as compared with the other atropine and scopolamine compounds mentioned in the present paper, is appended (table 2).

2. Clinical studies.

The fact that the new agent, methylscopolamine nitrate, does not have the inhibitory effect on the central nervous system ordin-

Table 2.

Relative effects of certain atropine and scopolamine compounds on the functions of different organs.

Substance	Chemical constitution	Relative toxicity in white mice	Relative inhibition of the salivary flow in man	Relative mydriatic effect in man	Relative antispasmodic effect on guinea-pig intestine	Inhibition of the cardiac vagus in man	Inhibition of the central nervous system in therapeutic doses in man
Atropine sulphate	Trivalent nitrogen	1	1.0	1.0	1.0	+	—
Methylatropine nitrate	Pentavalent nitrogen	3	2.2	1.3	2.0	+++	—
Scopolamine hydrobromide	Trivalent nitrogen	1	3.0	3.0	0.6	—	+++
Methylscopolamine nitrate	Pentavalent nitrogen	3	3.6	3.0	5.5	+++	—

rally produced by scopolamine hydrobromide while at the same time the spasmolytic effect on the vegetative system in the intestines of animals is increased tenfold, obviously justifies the testing of the substance on clinical material. The increased toxicity which has been observed in animal experiments, similar to that found in connection with atropine and methatropine, is in all probability of little practical significance, with the doses employed. As in the case of atropine, larger doses of the new agent have a stimulatory effect on the central nerves.

Up to the present, the extent of the clinical trials has been limited. It goes without saying, also, that experiences from an agent with such a wide field of application as one exercising an antispasmodic effect on the vegetative system can only be gathered by degrees. Furthermore, we are dealing here with a type of treatment in which it is often difficult to establish and estimate the objective effects. It seems to me, however, that the agent has been of value in thirty odd cases of ulceration in which I have tried it, the dose used — $\frac{1}{2}$ mg. $\times 2-4$ — having in almost every instance brought freedom from pain and caused no after-effects when applied in conjunction with the other treatment. In a few cases of suspected or established gallstone, also, it had a noticeable effect

when injected in a dose of 0.2—0.3 mg. Leander (1944), in connection with a review on the evacuation of the urinary bladder from the aspects of pathologic physiology and therapy, stated that he had found the agent useful in a few cases of spastic disturbances of the bladder. Investigations on the usefulness of the substance for various purposes are in progress, especially in infantile pylorospasm.

Summary.

After reviewing the publications on the effect of the atropine alkaloids on unstriated gastro-intestinal muscle the author describes his own investigations in connection with a new drug, a methylscopolamine derivative (an N-methylated scopolamine with pentavalent nitrogen) which has proved in laboratory animals to have an antispasmodic effect on the vegetative system about five times greater than that produced by atropine sulphate and tenfold surpassing the effect of scopolamine hydrobromide in this respect. As the new drug does not have the inhibitory effect on the central nervous system shown by scopolamine hydrobromide, its powerful antispasmodic action on the vegetative system can be utilized in clinical medicine without risk of bye effects on the central nerves. The fact that, owing to the methylation, its effect on non-striated muscle is relatively stronger than other effects also facilitates the better utilization of this property. Encouraging results have been obtained from preliminary investigations on clinical material.

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On familiar constitutional fibrinopenia.

Some observations with regard to the simultaneous appearance of fibrinopenia, thrombopenia and hypoprothrombinemia.¹

By

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Introduction.

Hemorrhagic diathesis caused by fibrinopenia is still diagnosed so rarely, that every case ascertained with certainty has a claim for publication. The same holds good to a still higher degree with regard to the combination of fibrinopenia with a transitory or permanent thrombopenia, a phenomenon which is certainly in no way unknown in the hematologic literature (Opitz and Silberberg, Risak, Macfarlane, Glanzmann, Steiner and Keller, Hauser, Dam, Larsen and Plum), but to which the said authors do not seem to have paid any special attention. In a previous work (Nord. Med. 20. 1697, 1943) I myself have had an opportunity to prove the connection between the blood platelets and the fibrine values, which is found in cases of severe injury to the parenchyme of the liver, as appears in the case of a chronic hepatitis and hepatic cirrhosis. The conclusion of the work was, that simultaneously reduced blood platelet values and fibrine values for all practical purposes were an undecipherable proof of the presence of a parenchymateous mesenchymal liver affection (this in contradistinction to the so-called ectodermal, epithelial liver affections, the hepa-

¹ Given as a lecture before «The Danish Society for Internal Medicine» 2. 5- 1944.

tos). An account was given of the utilization of the phenomenon in the liver diägnostication. In the work mentioned, however, it was expressly emphasised, that there is in no way any question of a compulsory coupling between the blood platelet values and the fibrine values.

A number of works from later years (Glanzmann, Steiner and Keller, Freudenberg, Dressler, Hauser) have quite surprisingly and apparently somewhat uncomprehensibly given information about favourable effects of the K-vitamin in certain hemorrhagic diatheses, which were contingent on thrombopenia, thrombasthenia and fibrinopenia. The authors mentioned state, that the favourable effect consists in a normalizing of the bleeding time, the clotting time and the clot retraction, whereas the thrombopenia and fibrinopenia, which form the basis of the disease exist unchanged. Hauser demonstrates the rather frequent combination of absence of prothrombin and thrombopenia (values 58,000—54,000—89,000—63,000—107,000—2,560) in newborn children with differently formed courses of mb. hemorrhagicus neonatorum and finds a favourable effect of a K-vitamin supply (Synkavit), also in some cases, where a thrombopenia was present. After this Hauser considers the employment of the K-vitamin in cases of thrombopenia and thrombasthenia to be justified.

Dressler finds a reduction in the bleeding time during the Synkavit treatment in a case of thrombopenia (blood platelet values 10—30,000), where the clotting time and the prothrombin time were normal. Synkavit was given in very large doses, up to 8 ampullæ intravenously every time. Freudenberg is of the opinion, that the contents of fibrinogen may also be effected by very large doses of Synkavit. Especially Glanzmann, Steiner and Keller, have mentioned the transitory thrombopenia during acute hemorrhagic diatheses, which besides does not belong to the so-called thrombopenic group.

Own researches.

In the following I am going to state some observations with regard to 2 cases of hemorrhagic diathesis, contingent upon essential, familiar fibrinopenia. On the background just mentioned these cases give occasion to further reflections on the relation

between fibrinopenia, thrombopenia and hypoprothrombinemia. The hemorrhagic diathesis of fibrinopenia is as well known a latent one and does not become manifest until some trauma occurs, e. g. tooth-drawing, parturition, menses, and in newborn it may for i. cause afterbleeding from the stump of the umbilical cord.

Case records. The patients in question are brothers, nr. 3 and 4 respectively of 4 brothers and sisters. Nr. 1 a girl, died at birth nr. 2 a girl 5 years old, is healthy and has never offered any sign of a hemorrhagic diathesis.

No known dispositions in the father's family, especially no hemorrhagic diathesis. The mother has 9 brothers and sisters, 4 men and 5 women. A brother has suffered from protracted bleedings from the nose during his childhood and youth, this had decreased considerably during adulthood, a sister is likewise greatly disposed for bleeding from the nose, and 2 years ago hypoprothrombinemia was demonstrated in her (P. Plum). All the other brothers and sisters and the mother herself are perfectly healthy and they do especially not offer any sign of a hemorrhagic diathesis. The family being resident at Bornholm no systematic examinations have been possible.

Patient nr. 1. ♂ E. R., born 8/3 1940. r. 150/IV—1940, admitted 29/3—4/4 1940. Mature birth, weight at birth 3 200, breast-child.

When the navel fell on the 7th day, bleeding commenced from the place, an oozing bleeding was present for a few days, for which reason he got an injection of K-vitamin preparation on the 9th day, since there was no bleeding. Got, however, further for the next 10 days K-vitamin tablets daily. On the 21st day of life the prothrombin time was determined as $R = 2.2$, which is a reduced state (R is reversely proportional to the contents of prothrombin, normally between 1.3 and 0.7 — Dam and Glavind). At the same time a fibrine determination showed 0.14 p. c., and the child was admitted to the department G of the R. H.

At the admittance there was a little bleeding from the various places of blood taking, but otherwise he did not offer any sign of a hemorrhagic diathesis during the stay at the hospital. General conditions were good, and he was discharged in a state of normal growth.

Patient nr. 2. ♂ P. R., born 15/11 1942. r. 711/XI—1943, admitted 24/11—8/12 1942 and 23/11—29/11 1943. Mature birth, weight at birth 3 100, breast-child.

No particular bleeding at birth, a white infarct was present in the placenta.

On the 7th day it was observed, that the child was bleeding from the navel knocked off. 2 cm³ of Kvitazol is given. As some oozing bleeding is still keeping on, kauterization is first made, and then a hemoclaudent tampon is fixed, but at last it is necessary to make a restitching, and the bleeding stops. The prothrombin time is on the following day determined by Larsen and Plum's method at 120 sec. (normally 18—20 sec.) and hb. p. c. = 76, for which reason the child is admitted to the department G. of the R. H. Here he was not exhausted, drank quickly and did not later on offer any sign of a hemorrhagic diathesis, but the prothrombin time remained at an increased level (51—46—51 sec.), for which reason 1 tablet of Soluchinon was further given on the 18th day of life. There was a moderate, rather quickly-disappearing icterus neonatorum. Was discharged in a state of good growth, but still with a rather pronounced anaemia. Hb. p. c. = 68.

Grew well during the following year and offered especially no signs of a hemorrhagic diathesis. When the child was 1 year of age, the mother applied to the out-patients' department for children's diseases of the R. H., and caused by phimosis dilation of the prepuce was made with a Lister's pair of tongs. Immediately after this small operation only a slight bleeding was seen, but during the day a rather considerable oozing bleeding appeared from the preputial fold, so that altogether 5 diapers and trousers were well drenched. Therefore the mother applied in the evening to the casualty ward, from which the child was admitted.

At the admittance general conditions were good, the child is somewhat catharrhal. The prepuce is edematous, on the underside is a bleeding, plane of the size of a pea. Touching is repeatedly made with perchloride of iron 50 p. c., and 1 cm³ of Soluchinon was given.

However, as the oozing bleeding keeps on for the first 24 hours, and the hb. p. c. has fallen to 59, 90 cm³ blood transfusion is given on the following evening intraosseously in the left tibia. At the same time some bone marrow is aspirated from the tibia for examination.

The number of blood platelets (Oluf Thomsen) is 20,000 immediately before the transfusion and on the following days 5,000—164,000—159,000.

Fibrine (Gram) is 0.057 p. c. in the plasma immediately before the transfusion.

The prothrombin concentration (Larsen and Plum) could not be determined with any certainty according to the methodics mentioned on account of the fibrinopenia, as no formation of clot was seen, not even by observation of the sample for up to 16 hours. On the days after the transfusion a small clotting was certainly formed after the expiration of about 10 minutes, but the main part of the blood sample had not coagulated after having been left for $\frac{1}{2}$ an hour.

No further bleeding appeared after the transfusion, and the child was discharged after the expiration of 7 days, perfectly quick, but still slightly anaemic, hb p. c. 80.

The *afterexamination* of these two patients $3\frac{3}{4}$ years and 2 months respectively after the acute hemorrhagic diathesis showed two boys of natural appearance, somatically and psychically developed corresponding to their ages.

Clinically they did not offer any sign of a hemorrhagic diathesis, and neither had they done so during the intermediate period. Patient nr. 1 had suffered somewhat from strophulus and offered at the examination a rather severe pityriasis, patient nr. 2 had had some inclination for bronchitis.

Hematologically the following findings were made:

Table 1.

	Pat. nr. 1 ♂ E. R.	Pat. nr. 2 ♂ P. R.
Hb. p. c.	80	78
Leucocyt.	5,460	18,530
Diff.	nat.	nat.
Blood plat.	73,000	167,000
Fibrine p. c.	0.029	0.035
Prothrom. p. c.	63	42

Consequently this examination shows, that the hemorrhagic diathesis is still latently present — so as it is the rule in the case of an essential fibrinopenia — as there is an even excessive fibrinopenia and a considerable reduction in the prothrombin concentration, just as the blood platelet values in the one case is decidedly too low, while in the other case they are at any rate placed at the bottom limit of normality.

This phenomenon, *the combined reduction in the contents of the blood of fibrine, prothrombin and blood platelets in a latent phase of a so-called fibrinopenic, hemorrhagic diathesis, has not been ascertained previously.*

The bone marrow.

Schönholzer in a case of fibrinopenia in a 12 years' old boy has performed bone marrow puncture immediately post mortem; the findings were: A normal erythropoiesis, a myelocytaric displacement to the left and a heavy reduction of the plasma cells. Beyond these findings no research on the conditions of the bone marrow

in the case of an essential fibrinopenia has been published hitherto in the literature accessible, but these conditions are not without interest, as the place of formation of fibrinogen is still in no way accounted for. In one of the patients mentioned here (nr. 2), where an intraosseous blood transfusion has been made, marrow was aspirated before the transfusion for examination. The findings were:

Preparations for smoothing rather rich in cells. Strikingly great quantities are found of lymphocytes (59 p. c.), even when considering the age of the patient. Far the greater part of the lymphocytes present are small, mature forms, but some large, immature forms are found. The quantity of neutrophilely granulated cell forms must be characterized as rather plentiful in consideration of the great number of lymphocytes, whereas the number of erythroblasts seems to be strikingly small (7 p. c.). The differential count shows otherwise no abnormality. Scattered in the preparations moderate quantities of plasma cells are found, often in rather large crowds, which is rather exceptional, when due regard is taken to the patient's age. Along the borders and at the end of the smooth-preparation ample quantities of blood platelets are found in large crowds. Megacaryocytes are likewise chiefly found along the borders apparently in natural quantities, and morphologically they do hardly offer any abnormalities, however, it is to be specially mentioned, that some megacaryocytes and megacaryocytic nuclei are found surrounded by platelets, but it is possible, that such platelets surrounded by megacaryocytes are seen in somewhat smaller quantities than normally.

Bone marrow punctate rather rich in cells with a considerable lymphocytosis and somewhat reduced erythropoiesis, but without other certain abnormalities.

Harald Gormsen (sig.)

As the finding for the present is an isolated phenomenon, it should not here give any occasion to further comments. It is only to be pointed out, that at the afterexamination an anaemia was really present in both patients, just as they formerly were discharged from the department with anaemia, which indicates, that the reduced erythropoiesis is a reality.

On the technique of the prothrombin determination.

Dam, Larsen and Plum have shown, that the limit of the formation of a firm clot is found at a fibrine quantity in the plasma of about 0.06 p. c. Larsen and Plum's modification of Quick's principle of the prothrombin determination will therefore, as emphasised by the author, fail, when a severe fibrinopenia is

present. In order to counteract this the prothrombin contents were determined at the afterexamination by a modification of Thordarson's methodic for the prothrombin determination employable on capillary blood, which is stated in Acta Med. Scand. 115—41—43 by P. Plum.

The principle of this method is, that the clotting time is determined for a fibrinogen containing plasma free of prothrombin, which further contains kinase and calcium in optimal quantities. This system coagulates at the adding of prothrombin. The speed is only depending on the quantity of the prothrombin added.

The reagents necessary are:

I. *Prothrombin-free plasma*, which is obtained in the following way: Blood from a normal person is emptied by a venal puncture in the proportion of 10 mg of kalium-oxalate to 5 cm³ of blood. Then centrifuging, pipetting off of the plasma and adding 1/10 vol. AL(OH)₃. Then shaking and new centrifuging and pipetting off, after which the prothrombin is adsorbed from the plasma.

II. *Kinase solution*. 1 kinase tablet (Ido) to 5 cm³ of physiological saline.

III. *Calcium solution*. The concentration of 1.6 p. c. CaCl₂, 2H₂O are ascertained by experiments to be the optimal one.

IV. *Oxalate-medinal buffer solution*. To the medial buffer solution used by Thordarson (Dissert. p. 75) 0.2 p. c. kalium-oxalate is added.

Before commencing the execution of the experiment the following 2 things must be ascertained:

1. *That the prothrombin-free plasma is really free of prothrombin.*

0.1 cm³ of prothrombin-free plasma

1 drop of kinase

25 mm³ of a calcium solution

When left for 1 hour at least in waterbath at 37° no coagulation must appear.

2. *That fibrinogen is present in the prothrombin-free plasma.*

0.1 cm³ of prothrombin-free plasma

1 drop of kinase

25 mm³ of a calcium solution + a little hemoclaudent

Must be able to form a pretty clot in waterbath at 37° within a reasonable time (about 1 min.)

The actual test is made in the following way: After a good hyperaemisation of the heel (as the actual blood taking is of a decisive importance it is better never to use blood from the ear in case of babies) a rather deep cutting is made, so that a lively bleeding is obtained. With a special pipette 0.2 cm³ of blood is sucked up and immediately blown into a centrifuging glass containing 0.6 cm³ of oxalate-medinal buffer solution. Hereby the

dilution of 1 : 4 is obtained. From this dilution the dilutions of 1 : 8, 1 : 16 and 1 : 32 are further made. The dilution is made with oxalate-medinal buffer solution.

Now the clotting time is determined in the centrifugal glass (double determination for each dilution), and into the glass is pipetted off

0.1 cm³ of prothrombin-free plasma

1 drop of kinase

25 cm of a calcium solution

Mixing and 2 minutes' preparatory heating at 37°

0.1 cm³ of the plasma-dilution, the prothrombin concentration of which is to be determined, is added (also preparatorily heated for 2 minutes at 37°). The glasses are then turned in the waterbath every few seconds and the time of the formation of a clot is exactly taken down.

The calculation is made in the following way:

Blood dilution	Clotting time in sec.		The patient's contents of prothrombin in p.c. of the normal one
	Normal	Patient	
1 : 4	47 46 45	90 85 80	$\frac{46 \times 100}{85} = 54$
1 : 8	74 70 66	110 112 115	$\frac{70 \times 100}{112} = 63$
1 : 16	96 95 95	157 156 155	$\frac{95 \times 100}{156} = 61$
1 : 32	165 155 145	330 332 335	$\frac{155 \times 100}{332} = 47$
The result			56 p. c.

Discussion.

The present observation offers an example of the fact, that a typically familiar, essential fibrinopenia (i. e. without any detectable liver affection) may be connected with a transitory thrombopenia and a rather considerable hypoprothrombinemia, which has probably existed for many years.

As already mentioned in the introduction the combination of fibrinopenia and thrombopenia may easily be demonstrated in some previous works — also in such cases, where no manifest damage to the liver is found (Risak, Macfarlane, Dam, Larsen

and Plum). Thus the combination of the absence of prothrombin and thrombopenia is as mentioned also a reality, which is verified by Hauser and Freudenberg. The connection between the values of the blood platelets, the fibrine and the prothrombin ads itself as a natural link to previous observations.

The formation of the fibrinogen is as a rule put into connection with the liver, but on the other hand it is known, that fibrinopenia does not appear inevitably in liver-extirpated dogs (Eppinger). It is probably the contents of the liver of reticulo-endothelial tissue, which plays a rôle. The genesis of the blood platelets is fully mentioned in a previous work (1942) with examining of the relevant literature. The conclusion was, that the formation is probably made from the reticulo-endothelial apparatus of the organism, it was supposed at the transition from the undifferentiated mesenchymatous cell to the following links. Of the prothrombin it is said, that it is a protein substance of the globulin type (Astrup), which is supposed to be formed in the intact liver.

Modern hematology considers to a higher degree than formerly the different changes in the peripheral blood (i.e. the different blood diseases) as different manners of reaction from the very same system: The mesenchymatous, hematopoietic apparatus of the organism (Nordenson). A thrombopenia for inst. never signifies an isolated damage to the hematopoiesis and is not a symptom that may stand alone, some basic defect is always hidden behind, which may very well also be of interest to the formation of the fibrinogen and the prothrombin.

In other words, a single organ (here the liver) is often wrongly placed in the limelight, when really it is a question of an affection of a part of this organ, even if it is an integral part of it (the reticuloendothelial system). When these facts are taken into consideration, the therapeutic results mentioned in the introduction, by which under K-vitamin treatment they succeeded in normalizing the bleeding time and influence the retraction of the clotting respectively in cases of thrombopenia are not far so incomprehensible as appears at first sight. By means of the K-vitamin treatment there is a possibility of interfering with a mechanism, the single part of which cannot yet be grasped.

Summary.

Of late years it has repeatedly been stated, that the K-vitamin treatment has had a certain effect, also in cases of thrombopenia and fibrinopenia in spite of the fact, that the thrombopenia and the fibrinopenia exist unchanged.

2 cases are mentioned here of essential, familiar fibrinopenia, in the one case the acute, hemorrhagic diathesis is combined with a transitory severe thrombopenia, both cases showed a pronounced hypothrombinemia existing for months and years. The bone marrow examination in the one case gives the clue for a slightly reduced erythropoiesis and shows a rather considerable lymphocytic preponderance.

The latent character of the fibrinopenia is emphasised. The correlation demonstrated between the values of blood platelets, fibrine and prothrombin is a fact supporting a unitarian genesis, probably from the reticulo-endothelial system of the organism, and it gives a stimulus to the prothrombin investigations and possible therapeutic experiments with the K-vitamin also in connection with fibrinopenial and thrombopenial hemorrhagic diatheses.

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The Bacteriology of Erysipelas in Clinical Light.

By

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Since Fehleisen's pioneer works it has been generally acknowledged that erysipelas is due to hemolytic streptococci. But there has been a great deal of discussion as to the further qualities of these streptococci, and investigations from the past 15 years have even unsettled the formerly generally held opinion of the pathogenesis of the affection, the idea of an allergic reaction as a decisive factor having gained increasing interest.

The general opinion as to the bacteriological conditions in erysipelas rests in the main on Fehleisen's investigations (1882). In 13 patients, 2 of whom post mortem, Fehleisen was able to demonstrate streptococci in or near the margin of the erysipelatous lesion. By experiments of isolation he found moreover that this streptococcus presented quite specific features, and finally he pointed out, by experiments on humans, that intradermal injection of streptococci brought about erysipelas.

The question of the specificity of the streptococcus erysipelatis became subject to animated discussions. But within the past 10 years or so it has been settled that, by the methods applied so far of differentiation of hemolytic streptococci, especially determination of groups and types ad modum Lancefield and Griffith, it is impossible to distinguish a special streptococcus erysipelatis. On the contrary serologically identical strains are often found at widely

different diseases, such as scarlatina, puerperal fever, angina, purulent lesions, and erysipelas.

Fehleisen's demonstration of streptococci in the lymphatic vessels of the skin in the marginal zone as a constant phenomenon in erysipelas seems to be based chiefly on microscopical investigations, as experiments of isolation are described as being difficult. But there is found no detailed account of the result for all the patients.

Achalme's (1892) description of the microscopical finding is in conformity with the one given by Fehleisen, but besides he gives an elaborate account of experiments with cultures taken from erysipelas patients from which he obtained growth in 6 out of 7 cases.

Birkhaug (1928) succeeded in isolating hemolytic streptococci in more than 90 per cent of the investigated cases by taking culture from the marginal zone of the affected skin area, whereas he got growth only in 45 per cent by taking culture from more centrally located areas. The culture was obtained by intradermal injection and aspiration of physiological salt-water.

Amoss (1932) on the other hand states that in no case did he succeed in isolating streptococci from erysipelatos lesions if there were found no purulent processes or traumatic wounds. But in some cases he was able to demonstrate their presence microscopically. However, there were found but few bacteria, scattered scantily in small nests about the tissue. In facial erysipelas he regards streptococcal infections of the upper air-passages, specially the paranasal sinus to be of vital importance, a view that is shared by Keefer & Spink (1936), Benzon (1938), and Thomas Anderson (1939).

The incompatible observations made by taking culture from the erysipelatos lesion itself in connection with the fact that constitutional and hormonal factors seem to be of importance has brought about that of late years the hypothesis has been advanced that the erysipelatos lesion should in an essential degree be conditioned by a local, allergic reaction on a bacteriological basis (Birkhaug, Amoss, Benzon). Birkhaug (1928) showed, by experiments of inoculation into patients having presented recurrence several times, that injection of bacteria-free streptococcus toxin could bring about typical erysipelas with the usual localization

even though the injection was made in another place. Amoss (1932) found in accordance with this that the skin of the affected regions was hypersensitive to filtrate from bouillon cultures of strains isolated from erysipelas. Here it is worth mentioning that Dochez & Stevens (1927) brought about allergy in rabbits by injection of filtrate of streptococci erysipelatis.

Interesting in this connection is the question whether in the case of recurrence the same streptococcus type is demonstrable at the different attacks. Thomas Andersen declared in 1939 that up to that year no investigations had been published with special reference to this question. We have not either in the literature at hand found special studies on this problem.

During our appointment to the Blegdamskøpshospital we decided to make an attempt at contributing to the solution of these questions, and we tried, therefore, to isolate streptococci from the infected skin area of patients suffering from erysipelas. However, in conformity with Amoss' results the question of obtaining growth from these areas caused us very considerable difficulties.

From Fehleisen's and other contemporary works one gets the impression that the erysipelatos lesion, at least certain parts of it, is so infected that in microscopical preparations the streptococci are seen to lie in chains in the subcutaneous tissue. Birkhaug as mentioned above claimed to have obtained growth from more than 90 per cent of the marginal zones of the examined lesions, and from works by Keefer & Spink it appears that these investigators were often able to isolate the microbe either from the lesion or from the fauces of erysipelas patients. Unfortunately they stated nothing as to how often they found it in one place and how often in the other.

Having arrived at quite different results in attempts of cultivation from the affection and more definite as to the occurrence of streptococci in the naso-pharynx in cases of erysipelas we have found it appropriate to present our rather considerable material. The isolated strains have been submitted to determinations of types and groups at Statens Seruminstitut, Copenhagen, but no other bacteriological investigations have been made. We hope that our experiences may be of use with regard to the procurement of material for a future, more thorough study of these interesting facts.

Own Investigations.

Our material has been selected from among the patients that within the period of 1941—1943 were treated in the Blegdamshospital under a diagnosis of erysipelas, whether this was the main affection or occurred as a complication of another disease, generally scarlatina. The above mentioned period is posterior to the one from which Flensburg has collected his material, so accordingly a brief survey of the patients will be given here.

A total of 315 attacks of erysipelas were treated within this period; a few patients go into the material 2 or 3 times having had several attacks within the above space of time. 207 were females, 108 males, i.e. a ratio of nearly 2 to 1, which corresponds exactly to the figures indicated by Flensburg.

188 times the lesion was found in the face or the capillitium, 127 times in other places, chiefly on the crus. The sex distribution is for facial erysipelas the same as for the entire material (34 per cent males), whereas the other localizations show a slightly greater majority of females (29 per cent males), which is probably due to the fact that females are more often than males affected by varicose ulcers of the leg.

The age distribution does not differ from the one known from previous investigations. There is a maximum for all localizations and for both males and females within the first 3 or 4 years of life, after which the disease is comparatively rare for a number of years, slightly different for males and females. As for the females the frequency increases within the decade of 45 to 55 years of age, and considering the magnitude of the age-classes this frequency can probably be said to remain unchanged for the rest of life. As regards the males the frequency begins to increase already by the age of 35 to remain unchanged after this age. The material gives no definite information of the relation between localization and sex. There is not, as might perhaps have been expected, found a relative increase in the cases of crural erysipelas with advancing years.

As an indeed very rough measure of the severity of the disease we have chosen the maximal temperature. However, this classification applies only to the 205 cases included in the proper mate-

rial, which constitutes the patients from whom it has been tried to isolate hemolytic streptococci. They are distributed as shown in table I.

Table I.

No fever or the condition unexplained	38.0—38.9	39.0—39.9	40.0—
13	37	85	70
6.3 %	18.0 %	41.5 %	34.1 %

We regard the material as one that is quite ordinary for a large city with good sanitary conditions, and consisting chiefly of light and moderately severe cases. This view is supported by the fact that the death rate was 9 out of 315 cases, or 2.9 per cent. The lethality was slightly greater for crural and corporal erysipelas than for facial erysipelas, viz. 6 out of 127 (4.6 per cent) and 3 out of 188 (1.6 per cent) respectively. But a review of the causes of death shows that this difference is in all likelihood due to a coincidence in the composition of the material. As the 9 deaths give a good illustration of the kind of patients that succumb to erysipelas a brief mention of their diagnoses will be made here.

Only 1 patient can be said to have died of the lesion, and that was a 40 year old male suffering from crural erysipelas — sepsis (hemolytic streptococci) — subfascial phlegmon — myocardiac deg. In all the other cases the patients were old or extremely weak patients in whom the erysipelas decided the final issue. 6 females: 1. 52 years of age. Emboly of pulm. art. — myocardiac deg. — crural erysipelas. 2. 58 years of age. Art. pulm. emboly — myocardiac deg. — adipositas — crural erysipelas. 3. 60 years of age. Arterioscl. of coron. art. — myocardiac deg. — pneumonia — facial erysipelas. 4. 70 years of age. Pyarthrosis of dxt. cubitus — chron. polyarthr. — myocardi. & renal deg. — facial erysipelas. 5. 79 years of age. Myocardiac deg. — bronchopneum. — crural erysipelas. 6. 82 years of age. Emboly of pulm. art. — univers. arteriosclerosis — myocardiac fibrosis — crural erysipelas. 2 males: 1. 70 years of age. Univers. arterioscler. — myocardiac fibrosis — cardiac incompensation — crural erysipelas. 2. 71 years of age. Myocardi. deg. — (sclerosis of coron. art.) — bronchopneum. — facial erysipelas.

The treatment was in practically all cases sulfanilamide or during the latter part of the period sulfathiazol in the usual doses. We have endeavoured to carry out our experiments of isolation as early as possible, preferably before the administration of the above-mentioned substances, but this has not been practicable in all cases. The material shows, however, that this is of no great import-

ance, as growth of hemolytic streptococci is not rarely obtained at least during the whole of the first week after the commencement of the treatment, and occasionally even 14 to 16 days after.

As mentioned above experiments of isolation of bacteria were carried out only on 205 out of the 315 patients. This is due partly to accidental circumstances (vacations, oversights etc.), partly to the fact that during our work we took an interest now in one, now in another particular problem, which was then studied in specially suited patients, whereas others were left out of account during such periods. What has been said above of the material as a whole applies fully to the 205 patients experimented on.

The experiments fall in 2 groups: partly with cultures from nose and fauces, and partly with cultures from the lesion itself. Each group will be described separately.

1. *Cultures from Nose and Fauces.*

These were obtained in the usual manner by means of a stick wound about with cotton wool which after having been led into the nose or rubbed against the posterior wall of the fauces was sent to Statens Seruminstitut, Copenhagen, where further isolation and determination of type was undertaken. Cultures were taken partly from patients with facial erysipelas, partly from patients with crural erysipelas. The results are seen in tables II and III. As a rule isolation was only tried once in each patient as early after hospitalisation as possible.

Table II.

	Facial erysipelas.				Crural erysipelas.			
	Number of cult.	—	+	+%	Number of cult.	—	+	+%
Nose:	97	73	24	25%	29	29	0	0%
Fauces:	117	84	33	28%	29	24	5	15%

Table III.

Facial erysipelas.

Cases in which cultures were taken from nose and fauces.

Number	97
Positive in one or in both cases	36 or 37%

It appears from this table that it is possible to isolate hemolytic streptococci either from the nose or the fauces in a little more than

$\frac{1}{3}$ of the patients suffering from facial erysipelas. This is no doubt somewhat more often than is seen in a normal material and it must be justifiable to presume that there is a connection between the finding and the disease of the patient. As to the erysipelas of body and extremities the relation cannot be made out on the basis of the present material. 15 per cent positive are more than the normal material generally contains (various authors: 3—10 per cent). But the material is so small that such a deviation is very well imaginable without there being necessarily a real difference. Thus we think it justifiable to state that in facial erysipelas the guilty streptococcus very often is localised in the nose or the pharynx. In crural erysipelas, on the other hand, we think it more probable that the finding of microbes in these places is due simply to a coincidence having nothing to do with the actual disease.

In 8 patients, 7 with facial erysipelas, 1 with crural erysipelas, there was occasion to take cultures during 2 or 3 attacks. The result is seen in table IV, which shows that in 2 out of the 3 cases in which growth was obtained from 2 periods of disease we had to do with the same well-defined strains (A 17 and G 16), while in the 3rd case the type of the streptococci could not be determined. In other words the finding seems to favour the hypothesis that in cases of recurrence it is generally the same streptococcus strain that causes the different attacks.

Table IV.

Localisation	Attack No. I		Attack No. II.		Attack No. III.	
	nose	fauces	nose	fauces	nose	fauces
Face....	—	—	—	—		
do	A 1	A 1	—	—		
do	—	—	—	—		
do	—	—	A 17	A 17	A 17	A 17
do	G 16	—	G 16	—		
do	A ×	A ×	A ×	A ×		
do	—	—	—	—		
Crus....	—	—	—	—		

Table V.

Streptococcus strains isolated from the nose or the fauces of erysipelas patients:

Group	A	A	A	A	A	A	A	A	A	G
Type	1	6	12	13	17 (23)	25	27	×	auto-agglut.	16
Number of times	4	4	1	1	14	1	1	18	2	3

2. Cultures from the Lesion Itself.

5 different methods were tried.

A. From wounds in the affection. (Once in each patient). By means of a stick wound about with cotton wool possible scabs were removed with great care, after which another cotton wool stick picked up a little wound secretion. This other stick was placed in bouillon at 37° C (98.6° F) for 24 hours, after which some of the bouillon was smeared on a blood-agar plate. Next the types of contingent hemolytic streptococci were determined in Statens Serum-institut, Copenhagen.

The result appears from table VI. The best chance of obtaining growth is had if it is possible to point out the original wound and take culture from this place, the chance is but small at varicose ulcers of the leg.

B. Aspiration of bulla fluid and pouring into bouillon was done 14 times. Often very great amounts of fluid were extracted, but in spite of that the tubes remained sterile.

Table VI.

Culture from wounds in the lesion.				
Nature of wound.	Number.	+	—	Remarks.
Traumatic	39	11	28	3 of the positive findings originated from different wounds in one pt., 2 from 2 wounds in another pt., and 6 from 6 different pts.
Varicose ulc. of leg	13	1	12	

C. Culture from abscesses in the lesion was obtained with a cotton wool stick 7 times, 6 times with a positive result. Culture was taken only once from each abscess, so we might possibly have obtained growth also in the 7th patient, if we had displayed some more energy.

D. Biopsy of tissue taken by means of a cylindric borer $\frac{1}{2}$ cm in diameter. (Once, but often 2—3 biopsies in each patient). Except for spraying with chlorethyl no disinfection was made in order not to kill possibly present streptococci. Biopsies were undertaken partly in the margin of the red zone; partly just outside it, and partly in the zone itself. Some of the pieces of skin obtained were placed in bouillon, others were comminuted in a mortar and smeared on blood-agar plates. From five pieces a small

bit was taken for microscopy. We never succeeded in finding bacteria in the skin preparations thus produced, nor did we find them by cultivation in these cases.

A total of 69 biopsies were made. 4 of these, namely 2 from one patient and 1 from each of two others presented growth of hemolytic streptococci.

E. Injection of bouillon into the lesion with ensuing aspiration and pouring into bouillon was tried 19 times, but it never gave growth.

Thus it appears that in our hands the results of experiments with isolation of streptococci direct from the lesion have proved extremely poor. The bacteria were seen with comparative certainty only in the cases in which there were found abscesses. From the injection-aspiration method, recommended by many investigators, we have obtained no satisfactory results.

In this connection it may be mentioned that biopsy did not in a single case give rise to suppuration, and not even to the slightest physical discomfort, but the wounds healed up just as in normal tissue.

Table VII.

Streptococcus strains isolated from the erysipelatous lesion.

Group.....	A	A	A	A	A	A	A	not determined
Type	1	6	17 (23)	25	27	31	×	not determined
Number of times.....	6	1	1	2	1	2	2	2

In a number of cases culture was taken both from the lesion, the fauces, and/or the nose. The cases in which growth was obtained from at least one of these places have been entered in table VIII.

Table VIII.

Facial erysipelas.

	Number.	Result.
+ n-ph — locally:	9	
— n-ph + locally:	4	
+ n-ph + locally:	2	Both: fauces A ×, orbital abscess A 1.

Crural and corporal erysipelas.

	Number.	Result.
+ n-ph — locally:	1	
— n-ph + locally:	3	
+ n-ph + locally:	1	Fauces: G 16, ulc. crur. varic: A 6.

It is seen that in the 3 cases in which growth was obtained both from the lesion and from the fauces there was not found the same streptococcus strain in the 2 regions. In one case we had to do with a patient suffering from crural erysipelas, where the relation between the finding of streptococci in the naso-pharynx and the occurrence of erysipelas must, also from other observations, be regarded as doubtful. The two cases of facial erysipelas are more difficult to understand because they contrary to our other results speak against the hypothesis that the streptococci in the naso-pharynx are of importance by this localisation. The explanation is perhaps this that by the time of the investigation there were or had been different streptococcus strains in the fauces, among which only one was isolated, and even one, that seems to have been of no significance for the onset of the erysipelas.

In 7 cases the erysipelas was a complication of suppurative otitis media. In 4 of the patients hemolytic streptococci were demonstrated, once both in ear, nose, and fauces, twice in ear and nose, and once only in the ear, always the same type in all regions.

Table IX.

Streptococcus strains isolated from erysipelas patients.

Group	A	A	A	A	A	A	A	A	A	A	A	G
Type	1	6	8	12	13	17 (23)	25	27	31	×	auto-aggl.	16

Discussion.

If the result of our experiments of demonstrating streptococci in the affected skin area itself is compared with those of earlier investigators it appears plainly that the former goes against the rather prevalent view that erysipelas is a kind of septic dermatitis. As stated above we did not in any one of the 5 patients submitted to our investigations succeed in demonstrating streptococci by microscopy of skin from the affected region. Culture taken from tissue removed for biopsy from the lesion itself gave growth only in 4 out of 69 cases, while culture obtained by injection and reaspiration of bouillon from the erysipelatosus lesion or from the bulla fluid in the latter; undertaken 19 and 14 times respectively, never gave any growth whatever.

No explanation can be given of the incongruity between Fehlei-

sen's and Birkhaug's results on one side and ours on the other. Misconceptions at the microscopy are hardly likely to have played any part, as Fehleisen's observations, which have also been corroborated by Robert Koch (1881), seem quite certain according to descriptions and accounts, and our preparations have not been difficult to conceive. Difference between the isolation technique applied by Birkhaug and the one applied by us is hardly either of any great significance. Possibly an exact knowledge of the patients submitted to investigation, with regard to the course of the disease and to a contingent occurrence of suppurant processes, might contribute to the elucidation. Such information has not been obtainable, however.

But by taking culture from the naso-pharynx of patients suffering from facial erysipelas we succeeded in demonstrating hemolytic streptococci in 37 per cent of the cases, and by taking culture from traumatic wounds that might be regarded as the points of entry, and from purulent processes in the lesion the microbe was demonstrated in 28 per cent and 86 per cent respectively.

Thus by way of summing up it must be said that our investigations favour the view that the hemolytic streptococci in erysipelas act primarily as a stirring factor in an allergic reaction, whereas the local occurrence in the lesion is of inferior significance, as the streptococci are either not found there or present only in very small amounts. The theory that in the case of recurrence it is the same strain that causes the attacks is supported by the fact that in 2 out of the 3 cases in which growth was obtained several times the streptococci were of the same type. In the third case the type could not be determined.

Finally our bacteriological investigations have fully borne out the view that there is found no demonstrable, specific streptococcus erysipelatis, as by determinations of groups and types it appears that the strains isolated by us comprise no less than 11 different types. (7 from the affection, 10 from the naso-pharynx).

It seems expedient on the basis of the reported and produced bacteriological investigations to review some descriptions of the course of erysipelas, as it might be possible in this way to get an explanation of the above-mentioned incompatible bacteriological findings. Thus it is of interest to make out whether erysipelas ran a more severe course in former days than now, and whether there

were found proper epidemics or endemics, especially in the hospitals, where the disease seems to have been rather dreaded.

Fehleisen's material consisted probably of patients that clinically corresponded essentially to ours, for he emphasized expressly the risk of confounding affections as diffuse phlegmons, sepsis, and lymphangitis with »pure» erysipelas cases. The case records were not reported in detail, however, so a more exact comparison cannot be drawn. But from the case records in Achalmé's (1892) great work on erysipelas it appears that a number of the patients presented a much more severe pathological picture than is now generally seen. This is due partly to the fact that there were several very debile patients, partly to the fact that the material seems to have comprised some cases with phlegmonous or other severe suppurative affections. Billroth (1862) on the other hand pointed out the relative mild character of the disease in otherwise sound individuals.

To make out whether a change towards a milder course has taken place here in Denmark we have made a calculation of the cases in the Medical Department of the Kommunehospital, Copenhagen, within the period of 1863—1883 in order thus to have a material with which to compare the one described by Sørensen from the Blegdamshospital 1884—1904 and our own material. The result is seen in table X.

Table X.

	Entire number	Average lethality	Variation
KH Med. Dep.	1991	6.28 %	2.0 %—12.4 %
Sørensen.	2955	9.37 %	4.6 %—15.6 %
Authors	315	2.9 %	

From this table we may conclude that within these three periods the disease must have run practically the same course. If we start from the lethality, the latter seems to have remained at fairly the same level until about 6 or 7 years ago, after which time it has decreased, surely in consequence of the treatment by chemotherapeutics.

The other problem suggesting itself is that of the contagiousity of the disease, specially investigations as to the occurrence of proper epidemics or endemics. Descriptions of such are not found in European literature within the epoche of our studies, except for some

From the Medical Clinic of Maria Hospital, Helsingfors.
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Experiments with injections of stomach extracts in pernicious anemia.

By

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(Submitted for publication May 9, 1944).

Introduction.

Castle's hypothesis demands, as known, a collaboration between an endogene ventricle factor and an exogene food factor to cause the antipernicious liver factor. His hypothesis is, at the moment, the most generally embraced, and the one that seems to explain most clearly the pathogenesis of the pernicious anemia. There are, however, some observations that are somewhat difficult to combine with Castle's hypothesis. Müller has, for instance, produced preparations effective in pernicious anemia from foetal liver. If Castle's hypothesis is correct there must be a question of a liver factor only originating in the mother organism as the foetus has no access to extrinsic factor. The excellent antipernicious effect, observed by some investigators, of preparations from different parts of the intestinal canal, seems to be difficult to fit into Castle's scheme at first. Meulengracht has, however, found, that the pernicious factor in the intestinal wall must be taken as a mixture of Castle's two factors or rather as an intermediary product of them. It is more difficult to explain by the aid of Castle's hypothesis, the splendid results in pernicious anemia with intramuscular injections of concentrated gastric juice, which have been obtained by

Table
Cases of erysipelas in

Year	Surgical Departments 1863—75 1. Dep. 1875—1883 1. + 5 Dep.					
	Hospitalized		Developed in Dep.		Entire number	Developed in Dep.
	Cured	Dead	Cured	Dead		
1863	0	0	5	2	7	100
1864	Hosp. + developed 47, 1 of which died					
1865	22	0	17	0	39	44.6
1866	51	0	21	0	72	29.1
1867	Hosp. + developed 45, 3 of which died					
1868	48	0	15	3 developed coincidentally	66	27.2
1869	10	7	20	0	37	54
1870	6	1	12	3	22	68.2
1871	6	0	22	1	29	79.3
1872	2	0	15	0	17	88.2
1873	0	0	11	3	14	100
1874	0	0	21	5	26	100
1875	13	1	6	4	24	41.6
1876	1	0	11	8	20	95
1877	3	0	7	1	11	72.7
1878	1	0	9	2	12	96.1
1879	3	0	13	1	17	82.3
1880	0	0	5	1	6	100
1881	2	0	14	0	16	87.5
1882	1	0	8	0	9	88.8
1883	0	0	3	0	3	100

With regard to the surgical erysipelas patients it is seen that since 1869 by far the great number of cases developed inside the Department (from this time on admission took place only in consequence of wrong diagnosis). Thus contagion from without has been of but little significance. Practically all the cases developed in connection with an operation. The epidemics of 6 to 8 coinci-

XI.

the Kommunehospital.

Medical Departments 2. + 3. Dep.					
Hospitalized		Developed in Dep.		Entire number	% Developed in Dep.
Cured	Dead	Cured	Dead		
13	1	0	0	14	0
Hosp. + developed altog. 74, 7 of which died					
39	3	0	0	42	0
43 Face 38	6 Face 3	0	0	49	.0
38 » 32	1 » 1	0	0	39	0
39 » 32	1 » 0	3 Face 3	4 Face 1	47	14.8
97 » 71	7 » 6	7 » 7	1 » 0	112	7.1
62 » 34	0	14 » 5	3 » 2	79	21.5
94 » 71	7 Face 3	23 » 17	7 » 4	113	26.5
83 » 56	6 » 2	13 » 7	4 » 1	106	16.0
70 » 33	5 » 3	6 » 4	1 » 1	82	8.5
87 » 57	1 » 0	9 » 7	1 » 1	98	10.2
100	6	6	0	112	5.36
96	5	6 5 developed in pure Dep.	0	107	5.61
116	7	5 2 developed in pure Dep.	3 from inf. Dep.	131	6.1
114	4	7 3 developed in pure Dep.	0	125	5.6
144	8	10 5 developed in pure Dep.	1 from pure Dep.	163	6.8
130	9	11 7 developed in pure Dep.	1 from inf. Dep.	151	7.9
128	7	8 6 developed in pure Dep.	3 2 from pure Dep.	146	7.5
105	4	8 5 developed in pure Dep.	2 from inf. Dep.	119	8.4
139	4	11 1 developed in pure Dep.	2 1 from pure Dep.	156	8.3

dent cases mentioned by various writers were probably caused by occasional contamination of instruments with hemolytic streptococci. The lethality of the «surgical» erysipelas was by no means particularly great and, as in the forms developed in other ways, exclusively dependent on the general state of health of the patient.

Thus a comparison between older and more recent materials seems to show that in Denmark the character of erysipelas has undergone no change within the past 80 years. Besides, there is every indication that the affection is only to an inconsiderable extent contagious, and that Fehleisen's statement that the lesion should swarm with bacteria can hardly hold good as regards the majority of the cases.

Summary.

It is shown that hemolytic streptococci can be isolated from the nose or the fauces in 37 per cent of patients suffering from facial erysipelas and from the fauces in 15 per cent of patients suffering from crural erysipelas. Cultures from traumatic wounds or purulent processes in the lesion gave growth in 28 per cent and 86 per cent respectively of the cases submitted to investigation, whereas cultures from pure erysipelatos lesions gave growth only in 5.8 per cent at biopsy and 0 per cent at aspiration *ad modum* Birkhaug. In none of 5 cases submitted to investigation did we find bacteria by microscopy of tissue removed for biopsy from the affected skin areas.

In 2 patients with recurrent facial erysipelas we succeeded with certainty in demonstrating that the type of the streptococci in the nose and throat was the same both times, in a third patient the type of the strain could not be determined. The total number of isolated streptococcus strains comprised 11 different types. (7 from the affection itself, 10 from the naso-pharynx).

A review of the literature and of the annual reports from the Kommunehospital, Copenhagen, shows that the character of erysipelas does not seem to have changed since 1863. Further it is shown that under civilized conditions the contagiousity of the disease is very inconsiderable.

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Wolff, Parkinson and White's Syndrome.

By

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(Submitted for publication May 15, 1944).

In 1930, Wolff, Parkinson & White described 11 cases of a peculiar electrocardiographic abnormality which was designated as bundle branch block with short PQ interval. As subsequently the designation bundle branch block has proved misleading, the affection is now most commonly designated as the WPW syndrome. The criteria of the lesion are entirely electrocardiographic and consist in an abnormally wide QRS complex at the expense of the PQ interval, with QRS being at least 0.1 second, while PQ must be under 0.12 second in at least 2 leads. The P waves must be normal. Patients with this electrocardiographic abnormality show often a tendency to paroxysmal tachycardia. The syndrome is found predominantly in apparently healthy young persons without other signs of cardiac affection, and the prognosis is reckoned to be favorable, in class with the prognosis of cardiac neurosis.

In the literature, about 170 cases of this kind have been described. In Denmark, as early as 1931, Warburg called attention to the existence of the syndrome, but so far only 5 cases have been described in this country — by Aastrup, Fr. Poulsen, C. U. Jessen, and Schierbeck (2 cases). In this paper we shall report altogether 45 cases from this country, namely: besides Aastrup's case, who was reexamined, and Poulsen's case, who has not been published before, 43 new cases, 27 of which were collected on

going through 6 years' case records from the Medical Departments A and B of the Rigshospital, and 7 years' case records from the Medical Out-patient Clinic (respectively 5, 5, and 17 cases). The remainder are accidental findings obligingly placed at our disposal on application to various colleagues: Warburg (4 cases), Baastrup (3 cases), Fr. Poulsen (3 cases), Aastrup, Brochner-Mortensen, Guldager, Poul Iversen, Kühnel, Kaj Larsen, Schou, and F. Wulff (each 1 case). On the background of the hitherto reported 170 cases, our material thus looks rather large, and is the largest one reported so far from one place. The material has been the subject of thorough analysis with a view to the clinical significance of the WPW syndrome as well as to the electrocardiographic changes — in order, if possible, to contribute to the elucidation of the pathogenesis of the syndrome. In the present work we shall deal with the more clinical aspects, and in a following paper we shall mention more particular electrocardiographic studies and, in this connection, enter into the question about the pathogenesis.

Frequency of the WPW Syndrome.

The modest number of cases — about 170 — that have been mentioned in the entire medical literature in the course of more than 10 years, suggests that the WPW syndrome is a very rare phenomenon. Table 1 shows the statements made by various

Table 1.

Frequency of the Syndrome as reported by Various Authors.

Authors	No. of patients in starting material	No. of these patients electrocardiographed	WPW syndrome found in	Frequency per 100 patients of starting material	Frequency per 100 electrocardiographed patients
Hartog	?	8000	2	?	0.025
Pohlmann	?	10000	6	?	0.06
Hunter, Papp & Parkinson	19000 ?	19000	3	0.021 ?	0.021
„ „ „	14000 ?	14000	8	0.057 ?	0.057
Franke & Vetter	?	13000	8	?	0.062
Own material, Dep. A	5103	3705	4	0.078	0.108
„ „ „ B	5059	5059	4	0.079	0.079
„ „ Out-pt. Clin.	24353	8410	17	0.070	0.202

authors concerning the frequency of the syndrome, and for the sake of comparison we have entered that part of our material that lends itself to calculation of the frequency.

The various authors give the frequency per 100 electrocardiographed patients and arrive in this way at rather different results — as was to be expected. For, no doubt, the extent to which electrocardiography is employed in the various medical departments is subject to very wide variation. The figures given by Hunter, Papp & Parkinson come from the Cardiac Department of the London Hospital, where presumably all patients are examined by electrocardiography.

As is evident from Table 1, in the two medical departments of the hospital we found the frequency of the WPW syndrome to be about 0.08 % of the total number of patients, and in the out-patient clinic a frequency of 0.07 %. This means that one instance of WPW syndrome was found in about every 1250 hospitalized patients, and one instance in about every 1430 out-patients. The frequency thus obtained is a minimum, as most of the patients were electrocardiographed but once and — as will be pointed out later — the appearance of the WPW syndrome is very often intermittent. So we are able to establish that in contrast to the previously prevailing view, the WPW syndrome is by no means a rare phenomenon.

It is rather interesting that the frequency of the WPW syndrome per 100 consecutive patients is the same in Deps. A and B and in the Out-patient Clinic in spite of the difference in the employment of electrocardiography in the three places (respectively about $\frac{2}{3}$, all, and about $\frac{1}{3}$ of the patients electrocardiographed). This might indicate that all cases of WPW syndrome are diagnosed on electrocardiography of all the patients presenting any suspicion of cardiac disease. It is more likely, however, that the frequency in the out-patient material really is greater than in the material of Dep. B, as it is reasonable to expect that electrocardiography of the remaining $\frac{2}{3}$ of the out-patients would reveal several symptom-free cases (see below, under Symptomatology). (But such an argument would not apply to Dep. A in relation to Dep. B, as the figures are so small that a possible difference may be accidental.) Also Hunter, Papp & Parkinson found the frequency of the syndrome greater in an ambulant material than in the hospital material.

Even if we reckon that the previous authors cited in Table 1 had electrocardiographed all the patients in their starting material, the frequency of the syndrome per 100 consecutive patients in our material will still be considerably greater than reported previously.

Sex and Age.

Previously the WPW syndrome was found about twice as often in men as in women. Our material comprises 22 males and 23 females, so that in this respect it differs from the ones reported previously. The great number of women in our material may be explained in part by the circumstance that the out-patients include about twice as many women as men. Of 8410 electrocardiographed out-patients, 2346 were men, 5164 women, and among these patients 6 men and 11 women presented the WPW syndrome, that is a respective frequency of 0.185 and 0.213 per 100 electrocardiographed patients. 6 of the women with the syndrome were referred to the clinic from the Lying-in Departments and Antenatal Clinic of the Rigshospital. Everything considered, we have to assert that our material as far as the frequency of the syndrome is concerned shows no definite sex difference.

As to the age of the patients, it is generally stated that the syndrome is encountered most often in younger people although it is met with in all age-classes. The youngest patient on record is a child, 3 weeks old (Nádrai), the oldest a man of 74 years (Franke & Vetter).

In our material the youngest patient is 7 years old, the oldest 74. The age distribution is shown in Table 2. In this connection it is to be mentioned that the cases in our material come from departments to which practically only adults are admitted, a majority of them over 30 years old.

The age recorded in Table 2 is the age at which the lesion was first diagnosed electrocardiographically. It will be noticed that 32 of the patients then were between 11 and 40 years. Most likely the affection commences even earlier. In most cases the diagnosis was made accidentally by electrocardiography performed for another purpose, while in other cases it was made at a juncture when particular conditions — *e.g.*, pregnancy or change to harder work — had provoked or aggravated cardiac symptoms; most likely the lesion had been present in a latent form for a number

Table 2.
Age and Sex Distribution of the Writers' Material.

Age (years)	Males	Females	Total
0—10	1	0	1
11—20	3	3	6
21—30	6	10	16
31—40	7	3	10
41—50	1	2	3
51—60	2	2	4
61—70	0	2	2
71—80	2	1	3
Total	22	23	45

of years, at any rate, in several of the cases. Evidence to this effect is afforded also by the patients' complaints of paroxysmal tachycardia, as it is reasonable to assume that the syndrome has been present at least just as long as the patient has been troubled with paroxysmal tachycardia.

Of our 45 patients, 17 gave a history of attacks which from their description had to be looked upon as unquestionable paroxysmal tachycardia. The average age of this group of patients at the 1. electrocardiogram showing the WPW syndrome is 38.2 years, while the average age at the first attack of paroxysmal tachycardia is only 22.5 years, so that the lesion may be assumed to have been undiagnosed on an average for about 16 years. Of the 17 patients with paroxysmal tachycardia, 2 stated this phenomenon had commenced at the age of 0—10 years, 6 at the age of 11—20 years, 7 at the age of 21—30 years, 1 at the age of 31—40 years, and 1 at the age of 41—50 years.

So there can be no doubt that the WPW syndrome makes its appearance preferably in the younger age-classes.

WPW Syndrome and Organic Heart Lesion.

On discussing the cause of the WPW syndrome it is of interest to look into the occurrence of other diseases in the past history of the patients, especially such affections as are known often to give rise to cardiac complications. In particular, it is important to

enquire whether such a lesion occurred in direct connection with the appearance of the WPW syndrome.

Most of the earlier authors thought that the WPW syndrome is due to a change in vagotonus or a congenital anomaly, whereas in recent years there has been a tendency to associate it with organic, acquired, affection of the heart. Hunter, Papp & Parkinson state that among the 90 cases of WPW syndrome published up to 1939, 18 presented signs of organic heart lesion, but only in 6 of these cases was there reason to assume a relation between this and the WPW syndrome. Among the 22 cases reported by Hunter, Papp & Parkinson (including 3 of Clerc's type, with short PQ interval and normal QRS) 3 presented definite signs of organic heart lesion, all rheumatic, and in 2 of these cases the WPW syndrome was diagnosed in immediate connection with an attack of rheumatic fever. In 5 other cases there was a possibility of organic heart lesion (1) hypertension, 2) lobar pneumonia, 3) positive Wassermann, 4) thyrotoxicosis, 5) died 1 year later of cardiac insufficiency). Master, Jaffe & Dack found the syndrome in a case of thyrotoxicosis, an here it disappeared after thyroidectomy. Also O. Jervell and Lamb have described the WPW syndrome in cases of thyrotoxicosis. Bain & Hamilton found the WPW syndrome in a patient with rheumatic carditis without valvular lesions. Of Hartlog's 4 patients one was suffering from hypertension, one from mitral stenosis. v. Zimmermann-Meinzig found the WPW syndrome in endocarditis lenta. Of Pohlmann's 3 patients 2 had congenital pulmonary stenosis, 1 (aged 64 years) hypertrophy of the left ventricle. v. Gruber encountered the syndrome in severe angina, Billmann in acute enteritis, Hamburger in acute infection of the respiratory passages (child, 4 1/2 years old), Fulchiero and Katz & Kaplan in coronary thrombosis, Schierheck in traumatic heart lesion. Although a number of single cases of WPW syndrome thus have been reported in relation to organic heart lesion, no other author has yet gone so far as Schubert who found that in nearly all cases the syndrome is due to organic heart lesion, as such an affection — often severe — could be demonstrated in 12 of his 17 cases. In another respect too Schubert's material differs from most other materials: the majority of his patients are elderly persons. As we have had no opportunity to see Schubert's electrocardiograms we shall refrain from any criticism of his material.

Although we think that the WPW syndrome may be acquired, it has to be recognized that in most of the above-mentioned cases no conclusive proof was given of a causal connection between the postulated cause and the WPW syndrome. As this syndrome often is symptom-free it may very well have existed prior to the infection or other organic lesion which in itself was an indication for electrocardiography and thus brought about the diagnosis of the WPW syndrome. There can hardly be any doubt that the syndrome may be acquired, and rather convincing evidence to this effect has been furnished by the cases reported by Machold, Nádrai, Franke & Vetter (Case 2) and Öhnell (Case 1, with autopsy). On the other hand, Nádrai has also reported another case (of a child 3 weeks old, with ranula) which indicates rather strongly that the WPW syndrome may be congenital. Most likely, then, it may be both congenital and acquired.

Writers' Material.

In Tables 3 and 4 we have recorded a number of cases in which the past history of the patients gives positive data on organic diseases that may have played a rôle in the origin of the WPW syndrome.

From Table 3 it will be noticed that no less than 7 patients, i.e., 15.6 % of our entire material, have had rheumatic fever and, in addition, 1 has had chorea, while 1 has had erythema nodosum (rheumatic?). This great frequency of rheumatic fever in the past history of the patients is not due to the circumstance that particularly many rheumatic fever patients have been electrocardiographed. For in all these cases but one (No. 28) the WPW syndrome was diagnosed at a much later point of time, and here the rheumatic fever was no indication for the electrocardiography which revealed the WPW syndrome. From Table 3 it is evident, however, that in some cases (Nos. 20, 28, 33, 43, and 44) there appears to be a certain relation between the rheumatic infection and the onset of cardiac symptoms or the diagnosis of the WPW syndrome. In one patient (No. 20) roentgenography during the attack of rheumatic fever showed a marked enlargement of the heart; unfortunately the electrocardiogram of this patient has been lost, but according to the description in the case records, it showed no delay in A-V conduction, preponderance of the left side, nega-

Table 3.

Survey of Histories of Patients with Reference to a Past History of Other Diseases, especially Rheumatic Fever.

Case No.	Disease. Age at onset	Age at begin. of paroxysmal tach.	Onset of other cardiac symptoms	1. electrocardiography. 1. diagnosis of WPW.
20	Rheumatic fever, 35 years.	No tachycardia	After rheumatic fever	35 years old
25	Rheumatic fever, 18 years.		After rheum. fev.	39 " "
	Exophthalmic goiter, 23 years.	No tachycardia	(After exophthalmic goiter)	23 " "
28	Rheumatic fever, 7 years.	No tachycardia	0	7 " "
30	Rheumatic fever, 18 years.	No tachycardia	«Many years ago»	74 " "
32	Chorea, 10 years (Diphtheria, 12 years)	45 years	0	65 " "
33	Rheumatic fever, 9 years	14—15 years	0	32 " "
				38 " "
36	Rheumatic fever «in youth»	No tachycardia	«2 years ago»	59 " "
43	Rheumatic fever, 13 years	«From boyhood»	0	39 " "
44	Erythema nodosum (rheumatic?), 30 years	Immediately after eryth. nodos.	Immediately after eryth. nodos.	34 " "

tive T_1 , diphasic T_2 and T_3 » so it may have been WPW; 4 years later the heart was found to be of normal size, and electrocardiography showed the presence of the WPW syndrome (Fig. 20). But none of the cases furnish any proof that the WPW syndrome is due to rheumatic infection, as it may have existed prior to the onset of the infection.

On the other hand, the great frequency of rheumatic fever (15.6 %) in this material may be taken as evidence of the causal significance of this infection. For the sake of comparison, it may be mentioned that in a hospital material of 305 patients with all sorts of medical diseases, including heart lesions, only 35 gave a history of past or recent rheumatic fever, i.e., a frequency of 11.4 %. These figures are too small, however, to establish any difference with certainty, and the basis for comparison is not quite definite. In

this connection it will be appropriate to mention too that Warburg states that of all young men summoned for military service not over 5 %, and probably only 2—3 %, have had rheumatic fever.

Table 4.

Survey of Histories of Patients with Reference to a Past History of Other Diseases, Rheumatic Fever exclusive.

Case No.	Disease. Age at onset	Time of begin. of paroxysmal tach.	Onset of other cardiac symptoms	1. electro-cardiography. 1. diagnosis of WPW.
1	Gonorrhea 6 times, last in 1933.	1933	0	1937
6	Diphtheria, 23 yrs.	3 wks. after diphth.	0	3 wks. after diphth.
7	Recurrent angina and tonsillectomy, 18 years	Immediately after tonsillectomy.	0	8 wks. after tonsillectomy.
8	Severe angina, 20 years.	No tachycardia.	2 months after angina.	2 months after angina.
9	Appendectomy, 27 years.	Immediately after appendectomy.	0	24 years after appendectomy.
14	Recurrent angina in childhood.	About 7 years old.	0	17 years old.
17	Exophthalmic goiter, 26 years.	No tachycardia	During exophthalmic goiter.	During exophthalmic goiter.
18	Angina and nephritis, 7 years.	2 months after nephritis.	0	14 years after nephritis.
22	Influenza, 28 years.	No tachycardia	2—3 weeks after influenza.	5 months after influenza.
27	Pneumonia, 39 years.	Immediately after pneumonia.	0	22 years after pneum. 23 years after pneum.
12	Diphtheria with myocarditis, 9 years. Scarlet fever, 10 years.	About 13 years old.	About 13 years old.	43 years old.

In Table 4 a number of cases are entered where paroxysmal tachycardia or other cardiac symptoms commenced in immediate or rather near relation to a lesion that had given rise to myocarditis. These cases too furnished no conclusive evidence about the

origin of the syndrome, which may have been present prior to the disease; and the cardiac symptoms, which are largely dependent on nervous factors, were perhaps elicited merely through the general debility associated with the disease in question. That this view deserves consideration is obvious from the fact that also pregnancy and parturition are able to elicit or aggravate paroxysmal tachycardia as was observed in 8 of our patients (Nos. 3, 5, 6, 8, 15, 16, 18 and 21). For development of myocarditis proper in connection with pregnancy and parturition is a rare phenomenon.

Particular mention is to be made of Case 22 as here we meet with rather definite evidence to the extent that the WPW syndrome may arise on the basis of myocarditis. This was the case of a man, 28 years old, who in February 1943 had an attack of fever for a couple of days, together with headache and nausea; 2—3 weeks later there were marked fatigue, functional dyspnea and palpitation of the heart. On roentgenography the heart was found to be enlarged and the first electrocardiogram showed the WPW syndrome; later this syndrome was found to alternate with various forms of disturbances of the auriculoventricular conduction.

All told, our material presents such essential evidence of the WPW syndrome being able to arise on the basis of acute myocarditis that we have to look upon this as most probable, without denying that the syndrome may be congenital too. Another observation which indicates that this syndrome may be acquired is, that in some cases (No. 1, 2, 7, 8) it cannot be demonstrated again on reexamination of the patient. But this observation is to be judged of only with cautiousness, because the WPW syndrome has a pronounced tendency to intermittent appearance. Observation of the material for a longer period may give additional information about this point. Considering Table 2, moreover, there can hardly be any doubt that the WPW syndrome disappears in a good many patients when they reach a more advanced age. For patients with a WPW syndrome do not die of this affection and the accumulation of cases in the younger age-classes where acute infections are particularly frequent, suggests very strongly that the WPW syndrome may be due to acquired organic heart lesion.

WPW Syndrome and Pregnancy and Parturition.

This question has been touched on already, but now it will be dealt with more thoroughly. Pines has reported an instance of WPW syndrome in a pregnant woman, 21 years old, but, apart from this, we have not been able in the literature to find any data on the relation between the WPW syndrome and pregnancy or parturition. Our material, as mentioned, includes 23 women, 2 of whom (Nos. 13 and 32) have never been pregnant. In 8 cases (Nos. 2, 9, 12, 17, 30, 36, 38 and 42) no data are available concerning pregnancy. In 4 cases (Nos. 25, 26, 27 and 29) data are recorded on pregnancy and parturition without any relation to the WPW syndrome. In 8 cases (Nos. 3, 5, 6, 8, 15, 16, 18 and 21) the records say that paroxysmal tachycardia arose or was aggravated in connection with pregnancy or parturition; and in 5 of these cases pregnancy or parturition was the occasion for the diagnosis of the WPW syndrome. In 2 cases (Nos. 6 and 18) the paroxysmal tachycardia was aggravated markedly during pregnancy, on which account induced abortion was recommended. Our material shows that only under these circumstances is the WPW syndrome to be taken as an indication for interruption of pregnancy, as at any rate 7 patients have gone through parturition without any trouble at a point of time when presumably they were suffering from the WPW syndrome.

WPW Syndrome and Congenital Malformations and Defects.

In view of the theory about the WPW syndrome being a congenital anomaly, it is of interest to look into the occurrence of congenital malformations in the present material. Altogether, 4 patients gave positive data on such conditions: pronounced congenital pes plano-valgus in one case, congenital club-foot in one, congenital hernia in two. Of course, these small figures allow of no conclusion. The frequency of congenital deformity of the foot in the total population is about $1-1\frac{1}{2}\%$. It is somewhat striking that 3 of the present cases come from a hospital for mental diseases and were diagnosed through the routine electrocardiography preceding shock therapy.

Complaints.

5 patients had no cardiac symptoms of any kind (Nos. 4, 28, 29, 39 and 42), and 10 patients with paroxysmal tachycardia had no cardiac symptoms whatever between the attacks (Nos. 9, 18, 24, 32, 33, 35, 38, 40, 41 and 43). The remaining patients complained of usually mild or moderate cardiac symptoms, namely: mild functional dyspnea in 20, palpitation of the heart in 25, slight discomfort of other character in the heart region in 11. Further, 13 complained of nervousness, 11 of tiredness, and 1 of chilliness of the hands and feet together with pronounced tendency to sweating. In all the cases, then, the cardiac symptoms were of a relatively mild character, similar to the ones encountered in cardiac neurosis. But the degree in which the patients were disabled was highly variable. From the aforementioned cases where the patient did not notice his heart at all or was inconvenienced merely during attacks of paroxysmal tachycardia there were all sorts of transitions to cases where the patient actually was disabled by greatly annoying cardiac complaints. Still, most of them attended to their daily work, often heavy manual labor, and others engaged in strenuous sports without any difficulty.

In the cases where the patient's physical capacity was lowered essentially, a nervous factor was plainly involved, and the present material illustrates strikingly that the degree of disablement with this affection is more dependent on the constitution and mental habits of the patient than on the heart lesion *in eo ipso*. Rather pronounced disability was encountered in 14 cases (Nos. 12, 13, 18, 20, 21, 22, 30, 31, 32, 35, 36, 37, 38 and 40), but 5 of these patients were elderly (Nos. 30, 32, 36, 39 and 40), and the possibility of some other affection (*e. g.*, coronary sclerosis) cannot be excluded as a contributory cause of the discomfort; in addition, one of these patients (No. 12) was also suffering from bronchiectasis, 1 (No. 20) had an unquestionable rheumatic heart lesion, 1 (No. 22) presented evidence of myocarditis after influenza, and 1 (No. 21) had been operated on for exophthalmic goiter. In other cases the disability was due to frequent and protracted attacks of paroxysmal tachycardia (Nos. 13, 18, 31, 32, 35 and 38). 4 patients were recommended for invalidity insurance benefit (Nos. 12, 20, 21 and 35),

but in 3 of these cases other complicating lesions were contributory to the disablement.

Paroxysmal Tachycardia. — Altogether 17 patients (7 women, 10 men) had attacks which, from their descriptions appear to have been typical of paroxysmal tachycardia. In 7 of these cases the tachycardia was registered cardiographically and found to be of supraventricular type in every instance. 7 additional patients had attacks which in all probability were paroxysmal tachycardia. The frequency of the attacks varied markedly, some patients having only a few attacks a year, whereas others had them at intervals of a few days. Also the duration of the attacks varied greatly, from a few minutes to several days; most often they lasted a few hours. In 2 cases the attacks were observed to last 3—4 weeks. In 5 cases they were so frequent and protracted as to disable the patient considerably.

In most of the cases the frequency and duration of the attacks kept rather unchanged throughout the observation period, which varies from a few days to 35 years. In a few cases the attacks increased in frequency with advancing age (Nos. 9, 35 and 40); in other cases they gradually decreased in frequency — as in Case 31, besides in cases Nos. 7, 14, 43, in which paroxysmal tachycardia occurred respectively for 7, 10 and about 20 years, whereafter there was no attack in the remaining observation period of 2, 2 and 10 years, respectively. As mentioned above, the material includes some cases in which paroxysmal tachycardia commenced or was aggravated during pregnancy or after parturition. In one case (No. 16) paroxysmal tachycardia was present for 2 years and aggravated during pregnancy, but after the parturition there was no attack (under observation for 1 ½ years post partum).

The attacks were elicited most often by nervous conditions, in some cases by physical exertion. In a few cases they were elicited by certain movements. In other cases they commenced without any known cause.

Objective Findings.

Apart from the electrocardiograms, objective signs of heart lesion were most scanty. Resting dyspnea and cyanosis were not found outside attacks of paroxysmal tachycardia. Enlargement

of the heart was found in 2 cases, namely: in patient No. 38, in whom paroxysmal tachycardia for 3—4 weeks was followed by severe cardiac insufficiency with enlargement of the heart and symptoms of stasis, terminating fatally, and in patient No. 40 who had acute myocarditis. In a third case (No. 19) enlargement of the heart had been demonstrated previously during an attack of rheumatic fever. In the remaining 33 cases in which the size of the heart was examined roentgenographically, it was found to be normal. Faint systolic murmurs were heard in 10 cases, spitting of the 2' sound in 1 case. The blood pressure was normal in all the patients but 5 who showed a systolic pressure over 150 mm; and these five patients were all elderly. Symptoms of stasis were found only in the above-mentioned patient No. 38 who died.

Electrocardiograms.

A total of about 300 electrocardiograms were taken. Figs. 1—45 show the extremity leads from each case, which were taken simultaneously in Cases 10—32, 35, 43 and 45.

As will be noticed, these electrocardiograms present at any rate 3 characteristic types, which we will designate as Types 1, 2 and 3. The first two are well-known from previous works.

Type 1. — This category includes Cases 1, 3, 5, 8, 11, 12, 21, 24, 30, 31, 32, 37, 40, 42, 43 and 45, which greatly resemble each other, and Cases 16, 26 and 29, which deviate a little from the others, altogether 19 cases. Characteristic of this fact is a marked left axis deviation in the QRS complex: a large R_1 , a smaller R_2 and, most often, an S_2 , together with a very large S_3 , which either is preceded by a very small R_3 or constitutes the only deflection in QRS_3 (see, for instance, Fig. 24). There may be some difference in the mutual proportion of the waves but in reality the electrocardiograms from these cases are surprisingly alike. As to RS-T and T, in 12 cases (Nos. 1, 12, 16, 21, 26, 29, 30, 31, 32, 37, 40 and 42) they show similar changes as are seen in pronounced left axis deviation, namely: negative (sometimes diphasic) T_1 and positive T_3 , together with a tendency in the RS-T sequence to shift in the same direction as the T waves, i.e., low RS- T_1 and high RS- T_3 . This indicates a pronounced delay in the conduction on the left side. As emphasized in a preceding paper, however, this does not necessarily mean an absolute delay in the conduction on the left side.

but merely a relative delay in comparison to the right ventricle, so that the same electrocardiographic changes presumably may arise through an abnormally early activation of the right ventricle. It is to be mentioned too that the changes in RS-T and T encountered in Cases 30 and 37 presumably are accentuated by digitalis.

I 6 cases of Type 1 (Nos. 3, 5, 8, 24, 43 and 45) T_1 is positive and T_3 negative; in 1 case (No. 11) all three T waves are positive.

Type 2. — This group comprises Cases 15, 19, 25, 27, 33 and 36, 6 cases. Characteristic of this type is the pronounced right axis deviation in the QRS complex: a large S_1 or a totally negative W-formed QRS complex in Lead I, besides large R_2 and R_3 . All 6 cases show a positive T_1 and negative or diphasic T_3 and RS- T_3 has a tendency to follow the T wave so that in Lead I it is a little elevated, in Lead III a little depressed. The electrocardiograms in these cases are characteristic of a pronounced right conduction delay or, in analogy to the preceding, merely a relative delay, so that it may mean an abnormally early activation of the left ventricle. In Case 36, presumably, the changes are accentuated by digitalis.

Type 3. — This group comprises Cases 9, 13, 14, 18, 28 and 39, i.e., 6 cases. Characteristic of this type is that the QRS complex is positive in all 3 leads, consisting of a large R wave; and the T wave is as a rule positive in all 3 leads (in a few exceptional cases it is flat diphasic or negative in Lead III). In Leads II and III the T wave in some cases is preceded by a slightly lowered S-T segment. In some cases (Nos. 9, 13, 14 and 18) this type deviates but very little from a normal electrocardiogram, the abnormality being manifest only in the very first part of the QRS complex. Presumably it is overlooked not infrequently.

Of the remaining 14 cases 2 (Nos. 7 and 22) present some special features. In Case 7 the WPW syndrome is recorded only in Lead I; before Leads II and III were taken, the WPW syndrome was again replaced by a normal rhythm, and hence the type cannot be classified. In Case 27 the electrocardiogram differs completely from all the other cases, reminding of the records seen in congenital heart lesions. This electrocardiogram was found in a case of acute myocarditis, alternating with electrocardiograms that showed pronounced disturbances in the auriculoventricular conduction.

The remaining 12 cases (Nos. 2, 4, 6, 10, 17, 20, 23, 34, 35, 38, 41 and 44) fall somewhat outside the three types described. In 4 of these cases the QRS complex shows a large Q_3 but is still to be reckoned rather as belonging to Type I, as QRS_3 approaches the totally inverted QRS_3 seen in some cases of Type I. The other cases show no changes in Lead III that are so pronounced that they may be classified after the above-mentioned typing.

In 28 cases the WPW syndrome was found in all the electrocardiograms taken (apart from the electrocardiograms showing paroxysmal tachycardia). It is to be mentioned, however, that in 7 of these cases only one electrocardiogram was taken. Otherwise, from 2—19 electrocardiograms were taken in every case in observation periods varying from 10 days to 16 years.

In the remaining 16 cases the WPW syndrome was found to vary with complexes showing normal PQ interval. In some cases, (for instance, Nos. 13 and 14) the WPW syndrome was alternating with a normal rhythm throughout the observation period. In other cases the WPW syndrome was observed at one juncture or other while subsequent electrocardiograms, often several years later, showed merely a normal rhythm (*e.g.* Cases 1, 2, 7, 8 and 41). Such findings have been emphasized previously as indicating that in several cases the WPW syndrome disappears with advancing age. This is in keeping with the age distribution of the material shown in Table 2, and it may be taken to support the view that the WPW syndrome often is acquired in connection with an attack of acute myocarditis in childhood or youth.

Course and Prognosis.

In our material one case terminated fatally: that of patient No. 38, who died after an attack of paroxysmal tachycardia that lasted 3—4 weeks and could not be checked, leading on to pronounced cardiac insufficiency. Previously this patient had had similar and protracted severe attacks with insufficiency, and in the intervals she had been feeling perfectly well. Thus we have to reckon with a certain, albeit slight, risk of death in protracted attacks of paroxysmal tachycardia, as they result in cardiac insufficiency if they persist long enough. Presumably this risk is minimal however, if all therapeutic remedies are employed. Apart from

this the prognosis is absolutely good, as the WPW syndrome presumably has no tendency to shorten the life of the patient.

The discomfort associated with the syndrome is chiefly dependent on the frequency and duration of the paroxysmal tachycardia. As to the course of the affection, therefore, it will suffice here to refer to what is said under the mention of paroxysmal tachycardia. Patients without paroxysmal tachycardia have no inconvenience other than those to which patients with cardiac neurosis are liable. It happens but very seldom that the lesion gives any discomfort in childhood. Most often the discomfort commences in youth, but the symptoms may not appear till the third or fourth decade, possibly because the disease in these cases has not been acquired before. No doubt several patients may go through life without noticing the affection at all.

Pathogenesis.

As to the pathogenesis we will here give merely a brief summary of the more important theories advanced and refer to the literature for details (*c.g.* Schubert and Hunter, Papp & Parkinson).

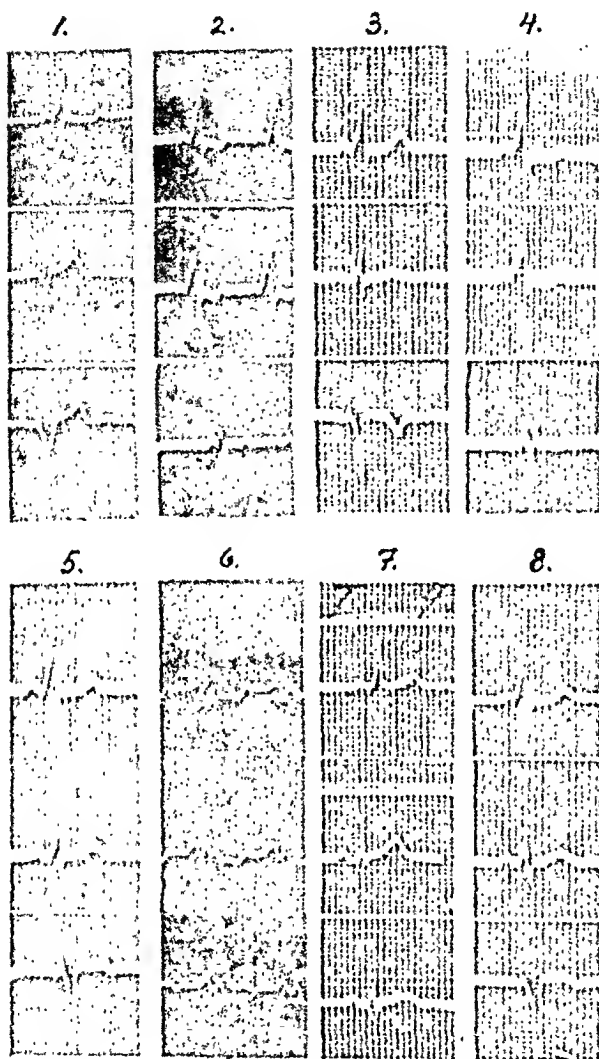
1. *Increased vagotonus.* This is the original theory, advanced by Wolff, Parkinson & White; it may be said to have been discarded.

2. *Kent's bundle.* This theory was advanced independently by Holzmänn & Scherf, and by Wolferth & Wood. It is based on the assumption of a congenital anomaly, as, besides the auriculoventricular bundle there is said to persist a connection between the right atrium and the right ventricle through which the stimulus would reach the right ventricle at an abnormally rapid rate.

3. *Nodal rhythm in connection with disturbance in the conduction through the ventricles,* which would explain the increase in the width QRS (Pezzi, Pines and others).

4. *Sinus rhythm with interfering extrasystole* (Holzmänn & Scherf, v. Gruber and others) and a modification of this theory (Hunter, Papp & Parkinson).

5. *Inhibited conductivity of the »sino-auricular» bundle together with inhibition of conduction through one branch of the bundle of His-Tawara* (Hauss & Schütt).

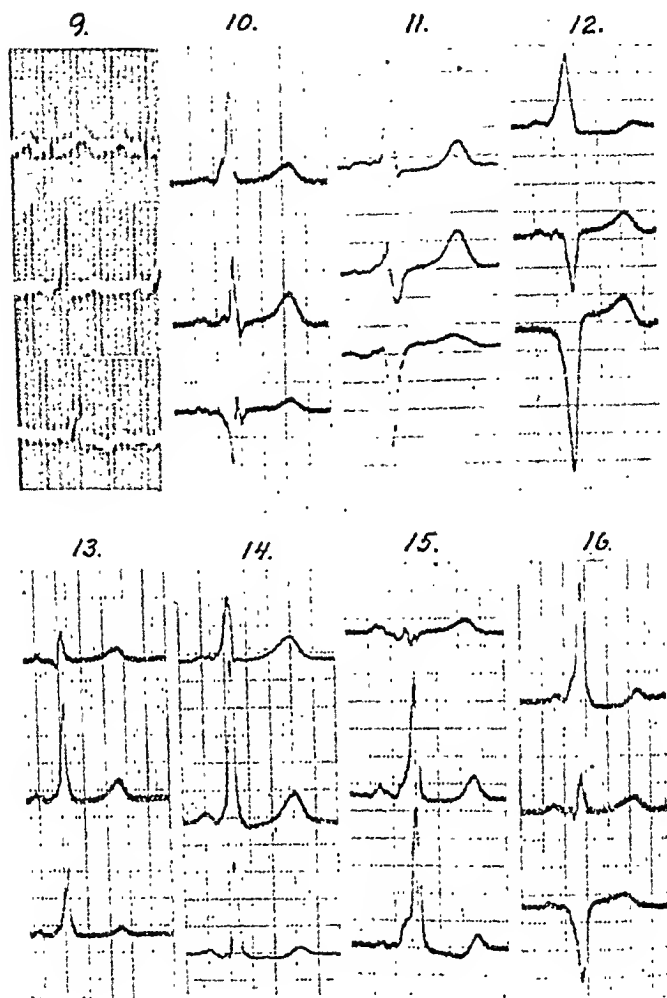


Figs. 1—45 show a section of an electrocardiogram from each of the 45 cases. The derivations from above downwards are Leads I, II and III. In Fig. 30 also a precordial electrocardiogram is taken.

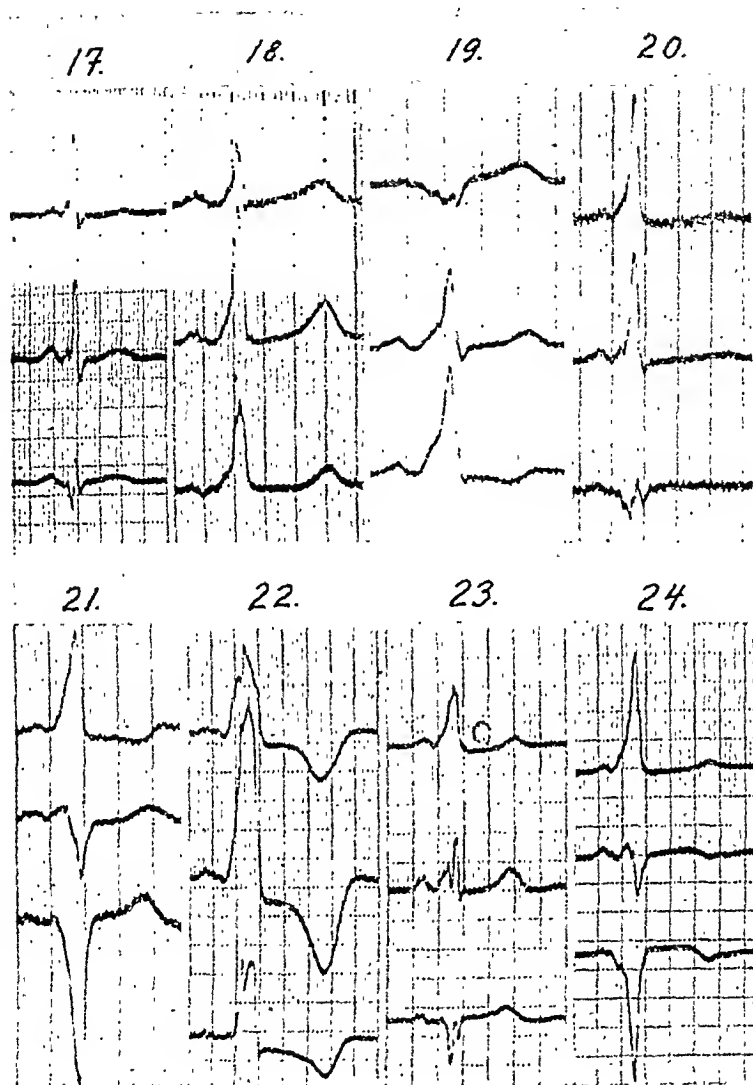
In Figs. 10—32, 35, 43 and 45 the derivations are taken simultaneously.

In Figs. 1—9 the time marker registers 0.04 and 0.20 sec.; in Figs. 10—32, 35 and 40—45 the time marker is 0.02 and 0.10 sec.; and in Figs. 33—34 and 36—39 it is 0.05 sec.

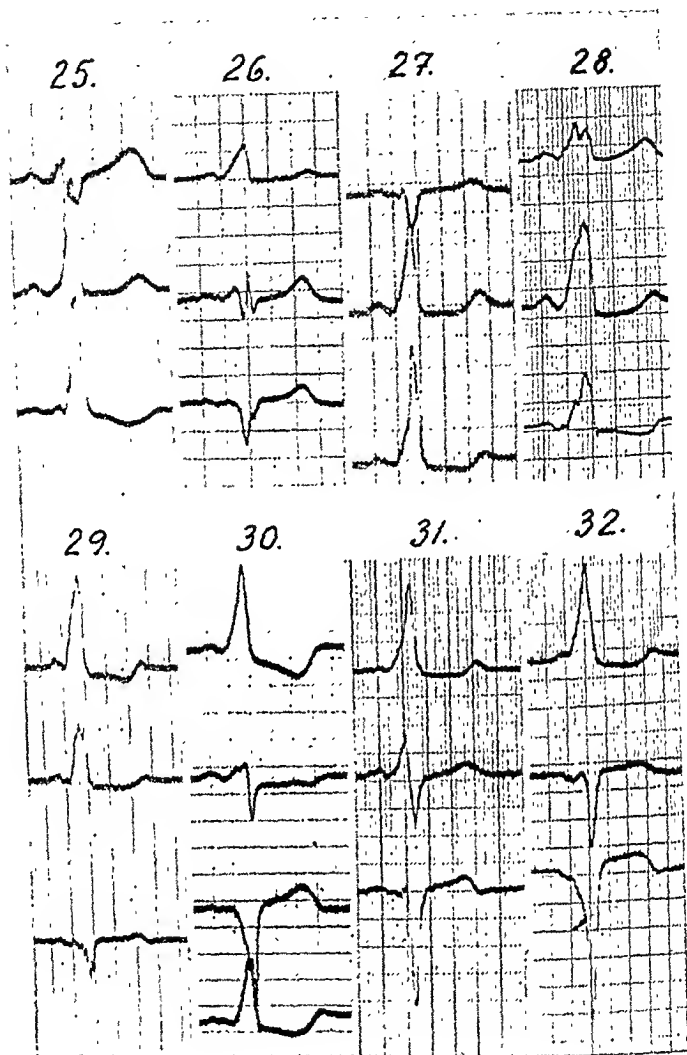
All the electrocardiograms are taken with such a sensitivity that 1 mV = 10 mm = twice the distance between 2 heavy horizontal lines.



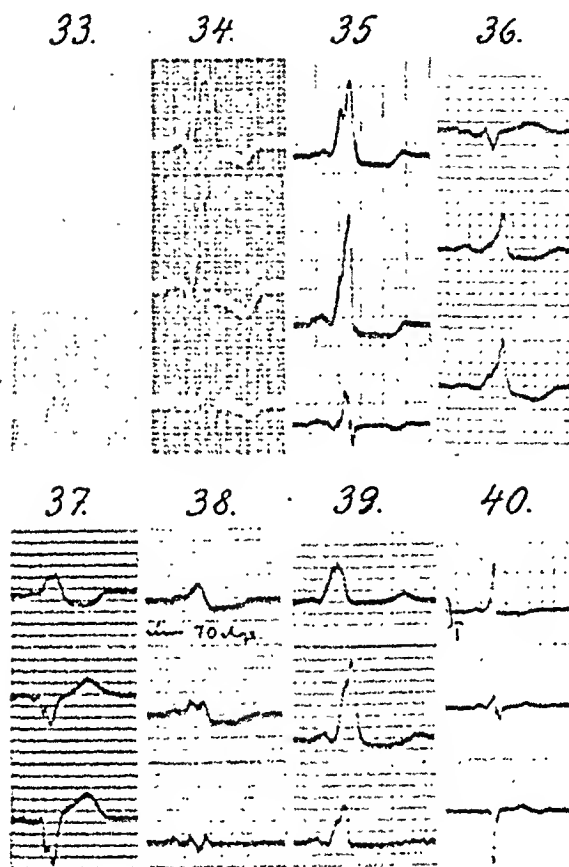
While the presence of the bundle of Kent is most problematic, Öhnell has recently reported a very interesting finding as in a case of WPW syndrome examined post mortem there was found an abnormal conducting bundle, more than $\frac{1}{2}$ cm long, which connected the left atrium and left ventricle. In another case Öhnell found inflammatory changes in the myocardium as the cause of the WPW syndrome. Pathogenetically, Öhnell thinks it is a matter of a special type of coupled ventricular extrasystoles.



According to our experiences we are rather inclined to subscribe to a modification of the above-mentioned theory No. 2, as we think that its two essential features may be looked upon as established, namely: 1) that it is a matter of a sinus rhythm and 2) an abnormally early activation of one of the ventricles. On the other hand, we find it very improbable that the WPW syndrome might be explained as attributable to such a well-defined congenital abnormal conduction tract as represented by the bundle of Kent, since both the electrocardiographic and the clinical features of the



lesion are too polymorphous to make this assumption reasonable. It may be that some cases are explainable in this way but in many other cases it is presumably a question of an acquired, abnormally conducting connection (scar formation after myocarditis or hæmorrhage?) that may be of greatly varied localization and thus give rise to considerable variation in the mutual activation of the ventricles and thus in the electrocardiographic picture. In a subsequent paper we expect to deal more thoroughly with this problem.



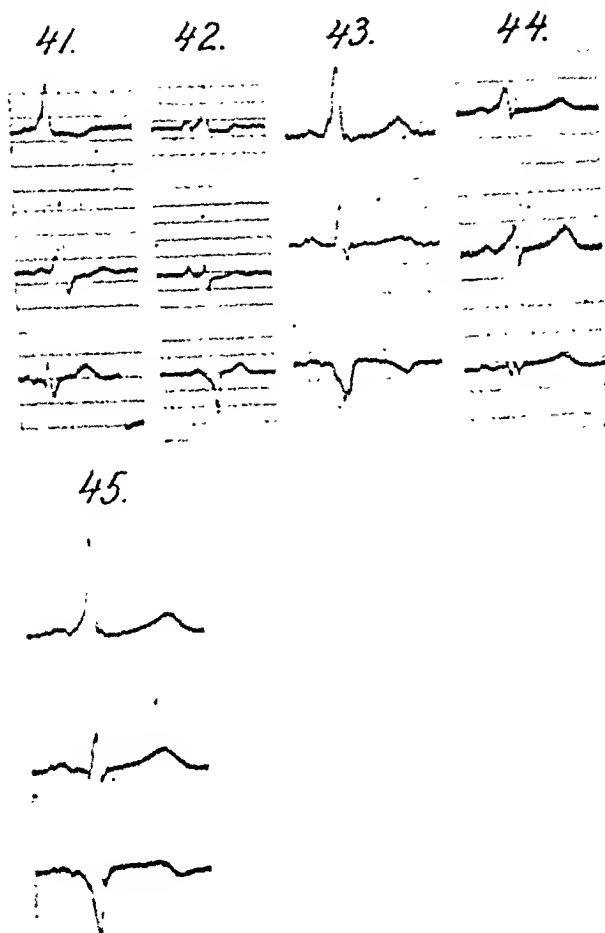
Summary and Conclusions.

The present material comprises 45 cases of the WPW syndrome, 43 of which have not been published before. The frequency of the syndrome is found to be considerably greater than given before and the same for men and women.

Like previous authors, we find the WPW syndrome, more frequent in the younger age-classes (up to 40 years), but it may be encountered in all age-classes.

Preliminary studies indicate that in several cases the syndrome subsides with advancing age. The accumulation of cases in younger persons, in whom acute infection are more frequent, suggests that the syndrome may be due to organic acquired heart lesion.

A past history of rheumatic fever was found in at least 15.6 %



of our patients. This, together with other data recorded in Tables 3 and 4, is taken to indicate that at any rate in several cases the WPW syndrome is acquired, having developed on the basis of myocarditis.

In 8 cases the WPW syndrome was diagnosed, or paroxysmal tachycardia had commenced or was aggravated, in connection with pregnancy and parturition.

Apart from paroxysmal tachycardia, the complaints in this lesion are mild and of the same character as those encountered in patients with cardiac neurosis. The inconvenience associated with the lesion is subject to very wide variation, from no complaint whatever to markedly disabling phenomena, depending on the constitution and mental habitus of the patient.

Paroxysmal tachycardia occurred presumably in 24 of the patients; it was recorded electrocardiographically in 7 cases.

Physical signs of cardiac disease occurred but seldom. The heart was enlarged in 3 patients, while roentgenographically it was found to be normal in 33. Hypertension was ascertained in 5 patients who all belonged to the older age-classes. Cardiac insufficiency was found only in 1 patient — after an attack of paroxysmal tachycardia that lasted 3—4 weeks. Otherwise physical examination revealed no changes of importance.

The electrocardiograms varied greatly and showed at any rate 3 well-characterized types: Type 1, with marked preponderance of the left side; Type 2, with marked preponderance of the right side; and Type 3, with positive QRS complex in all three leads. In 16 cases the appearance of the WPW syndrome was intermittent; in the remainder it was permanent.

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A simple method for the determination of the amount of liver glycogen in vivo.

By

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The praxis of liver biopsy inaugurated by Iversen and Rolholm (1) has led to a better insight in the histological changes which the liver undergoes under the influence of various diseases. It appeared at the same time that soon after death important alterations take place.

When the histological assay does not lead to the desired results, a biochemical study of the liver cells will perhaps in the near future provide us with the necessary indications regarding the nature of the disease. For this reason we have asked ourselves whether the study of these problems too might not be furthered by the introduction of the praxis of liver biopsy.

Glycogen, a very important constituent of the liver, was the first substance which we subjected to a quantitative investigation

It is well known that the glycogen content of the liver varies greatly, also that during the agony of death and the first hours post mortem glycogenolysis causes a considerable decrease, and that values obtained but a few hours after death accordingly are

unreliable. Our knowledge with regard to the liver glycogen therefore rests mainly on the quantitative analysis of small portions of the liver removed in cases of abdomen operations, and it is not impossible that under these circumstances the original value may have been influenced by the narcosis. At any rate, the opportunity to determine the amount of liver glycogen in cases in which the influence of disturbing factors might be neglected, was on the whole rare, and it is therefore of importance that we have now a simple method to obtain liver tissue *durante vitae*. It is not impossible that in several syndromes some insight may be obtained in the quantitative behaviour of this substance on which the attention so often has been focussed in this way.

The greatest difficulty evidently lies in the smallness of the available amount of liver tissue. However, it soon appeared that this is not necessarily a serious impediment.

For the estimation of the amount of glycogen Pflüger's method was followed. Of this several modifications have been introduced, of which Verheugt (2) gives a commendable survey.

Osterberg (3) described how the glycogen content may be determined in very small amounts of tissue (cf. ca 5 mg). The amounts available to us, varied between about 10 and 50 mg liver tissue. Obviously the determination is the easier the greater the amount of tissue. In several instances the size of the aspirate was sufficient for a determination in duplo.

Method.

The determination rests on the three principles laid down by Pflüger.

1° Destruction of the tissue by alkali, the glycogen remaining unaffected.

To a glass tube with ground stopper (see figure) 2 cm³ of a 30 per cent KOH solution is transferred by the aid of a pipette; after that the tube is weighed. The liver aspirate is freed, as far as possible, from blood, and brought in the tube; then the latter is weighed once more; the amount of liver tissue is found by subtraction. If possible, a second tube is used for a determination in duplo. The tubes are placed in a hot water bath heated to a temperature of 100° C, where they are left for two hours; they have to be shaken

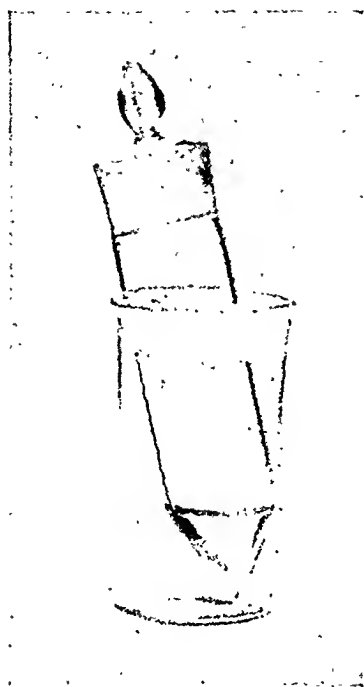


Fig. 1.

from time to time until the liver tissue is dissolved. The hot water bath may be replaced by a hot air stove heated to the same temperature.

2° Precipitation of the glycogen.

The tubes are cooled, and 8 cm³ of absolute alcohol added to the solution: the concentration of the alcohol decreases in this way to 80 per cent. After that the liquid is thoroughly stirred with a glass rod, which afterwards is washed with a 80 per cent alcohol solution.

The next day, to separate the precipitate from the liquid, the tubes are placed for 10 minutes on a centrifugal apparatus making 3000 revolutions per minute. After that the precipitate is washed three times with 5 cm³ of 65 per cent alcohol; each time the mixture is thoroughly stirred with a glass rod. Then it is dried on a hot water bath.

3° Hydrolysis of the glycogen in the precipitate to dextrose.

To this end 4 cm³ of a 2.2 per cent HCl solution is added. The tubes are now put in the hot water bath, where they are left for two or three hours. After the solution has cooled down, it is neutraliz-

Determinations made a long time after the adenoma had been removed, revealed a normal glycogen value (7.5 g per cent). Therefore, if there are indications pointing to this disease, a determination of the liver glycogen content may be possible regarded as a valuable test for the correctness of the diagnosis.

We also had an opportunity to determine the glycogen content of the liver of one patient suffering from myxedema. The value proved to be supranormal.

Patient	Glycogen in g per cent	B. M.
M.M.	12.36	— 20 per cent

To finish this account we will mention a few liver glycogen values obtained from patients with jaundice.

Patient	Diagnosis	Glycogen in g per cent	Heymans v/d Bergh (direct reaction)
D.	jaundice (due to carc. of the head of the paner). (After 3½ weeks)	3.8 —3.6	30 U
v.d.H.	subacute yellow liver atrophy, cause unknown; liver aspiration half an hour post mortem.	0.44—0.47	52 U
K.	Weil's disease; liver aspiration half an hour post mortem.	0.53—0.64	42 U
J.	liver cirrhosis	5.6	7 U

An interesting observation was made some time ago. Liver aspiration was performed 15 minutes post mortem on a patient who had suffered from acute yellow liver atrophy and had been treated with a dextrose infusion. The glycogen content of the aspirate was estimated by the aid of Best's staining method and proved rather large. From this it may be concluded that an important part of the liver cells in the aspirate of this patient must have been able to synthesize glycogen from the surplus dextrose. This function, therefore, had not been lost, as is commonly assumed.

Miss Cornelia van Beek had the kindness to study the histological slides made from all the patients mentioned above. The material had been fixed in 96 per cent alcohol and stained according to Best. The observation made by Nielsen, Fopp (5) a.o. that a trained eye can estimate the glycogen content in slides, stained in this way with a fair degree of accuracy, was confirmed. However, when the values increased above 4 g per cent, the estimation became impossible except e.g. in the slides made from the liver of the myxedema patient, which was exceedingly rich in glycogen.

At a subsequent occasion we hope to deal more extensively with the liver glycogen values present in various diseases.

Conclusion.

A simple method is indicated for the determination of the glycogen content of the liver *durante vitae*.

Examples are given.

As normal liver glycogen value 6 to 7 g per cent was found. In patients suffering from Morbus Basedowi or hyperthyroidism the values are low. In one myxedema patient a high value was found. The glycogen value of a patient who owing to an adenoma of the islets of Langerhans, suffered from spontaneous hypoglycemia, was low. Low values may also be present in patients suffering from hepatogenic jaundice, irrespective of the cause.

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Aus dem Pathologisch-anatomischen Institut der Universität Helsinki.
Vorstand: Prof. Dr. Arno Saxén.

Studien über den Diabetes mellitus in Finnland.

I. Die makroskopischen Organveränderungen der Diabetiker im Lichte des Obduktionsmaterials.¹

Von

ILMARI VARTIAINEN.

(Bei der Redaktion am 16. März 1944 eingegangen).

Die Zuckerkrankheit hat ihren Charakter im Laufe der Zeiten erheblich verändert. Obwohl sie schon im Altertum bekannt war, war sie damals doch so selten, dass auch die berühmten Ärzte sie nur einige Male gesehen hatten. In den letzten Jahrhunderten hat im Vorkommen dieser Krankheit eine Zunahme stattgefunden, die während der letzten Jahrzehnte z.B. in Amerika so stark gewesen ist, dass die Krankheit im Begriff steht, als Todesursache unter die ersten zu steigen. Die Zunahme ist in den hohen Altersklassen und bei den Frauen am stärksten gewesen. Joslin sagt denn auch dass der Diabetes, der eine Krankheit des männlichen Geschlechts und der Jungen gewesen ist, sich in eine Krankheit des weiblichen Geschlechts und der Alten umwandelt.

Im Vorkommen der »Nebenkrankheiten« des Diabetes haben ebenfalls bedeutende Veränderungen stattgefunden. Die Tuberkulose, die im vorigen Jahrhundert als Begleitkrankheit sehr gewöhnlich war, hat ab-, die Arteriosklerose wiederum zugenommen.

Die in der Behandlung der Zuckerkrankheit während der beiden vorausgehenden Jahrzehnte infolge der Entdeckung des Insulins und der protrahiert wirkenden Insuline eingetretenen Umwäl-

¹ Von einem Stipendium des Emil Aaltosen Säätiö-Fonds unterstützt.

zungen sind zweifellos ihrerseits danach angetan gewesen, den Charakter der Krankheit hochgradig zu beeinflussen.

Aber nicht nur hinsichtlich der Zeit sondern auch hinsichtlich des Ortes sind im Charakter der Zuckerkrankheit grosse Unterschiede wahrzunehmen. Die in irgendeinem Lande in bezug auf die Krankheit erworbenen Erfahrungen lassen sich nicht ohne weiteres in einem andern Lande zur Anwendung bringen.

In den meisten den Diabetes in den verschiedenen Ländern behandelnden Publikationen, Statistiken usw. ist Finnland wegen mangelnder Angaben unerwähnt geblieben. Meines Erachtens ist es wichtig, diesem Übelstand abzuhelpen. Ich beabsichtige deshalb, im vorliegenden die Diabetesfrage in Finnland mit den verfügbaren Mitteln von verschiedenen Seiten zu untersuchen. Zuerst behandle ich die pathologische Anatomie der Krankheit an Hand des Obduktionsmaterials.

Mit dem Aufstieg der pathologischen Anatomie zu einem der zentralsten Gebiete der Medizin in der zweiten Hälfte des vorigen Jahrhunderts, begann man auch den bei Diabetikeroobduktionen gemachten Beobachtungen mehr als früher Beachtung zu schenken. Schon um die Mitte des Jahrhunderts fingen die Pankreasveränderungen der Diabetiker infolge der Befunde des hervorragenden Forschers Bouehardat an, zum Gegenstand des Interesses zu werden. Nachdem die Bedeutung des Pankreas für die Entstehung der Krankheit durch die experimentellen Arbeiten von Merings und Minkowskis nachgewiesen worden war, konnte die eifrig betriebene mikroskopische Untersuchungsarbeit bald Veränderungen in den Langerhansschen Inseln aufzeigen. Es seien hier nur die Namen Ssobolew und Opie erwähnt. Obwohl die pathologische Anatomie der Zuckerkrankheit später wegen der gewaltigen Fortschritte in der Therapie der Krankheit ins Hintertreffen geraten ist, hat man doch keine Veranlassung, sie zu vergessen, denn sie ist vom Standpunkt der Totalität wichtig für das Verständnis der Krankheit.

Auch beim Untersuchen der »Nebenkrankheiten« des Diabetes kommt der pathologischen Anatomie eine wichtige Bedeutung zu. Man denke nur z.B. an die Erkrankungen der Gallenwege, die Arteriosklerose und die Tuberkulose.

Joslin unterstreicht in seinem Buch die Wichtigkeit der Diabetikerothduktionen und hält dafür, dass solche möglichst oft ausgeführt werden sollten.

Meine Absicht war zu untersuchen, ob bei den Diabetikerothduktionen Finnlands für die Zuckerkrankheit spezifische oder andere makroskopische Organveränderungen vorkommen und in welchem Masse.

Abgesehen von einigen früheren kurzen Erwähnungen von Obduktionsbefunden bei Diabetikern ist das Thema in der finnischen medizinischen Literatur nicht eigentlich behandelt worden, sodass ich die vorliegende Untersuchung als desto wichtiger betrachtet habe.

In diesem Zusammenhang möchte ich Herrn Prof. Dr. Arno Saxén, dem Vorstand des Pathologisch-anatomischen Institutes der Universität, meinen Dank dafür aussprechen, dass er mir das Material zur Verfügung gestellt und meine Arbeit mit Interesse geleitet hat, sowie Herrn Doz. Dr. Jaakko Tuominen für die Hilfe danken, die er mir bei der statistischen Behandlung des Materials hat zuteil werden lassen.

Material.

Die Diabetiker. Das Material umfasst die Sektionsprotokolle der im Verlauf von 50 Jahren (1894—1943) im Pathologisch-anatomischen Institut der Universität Helsinki obduzierten Diabetiker (i. J. 1894 war allerdings kein einziger Diabetiker obduziert worden). Alles in allem ergeben sich für die Diabetiker folgende Obduktionszahlen:

Vor der Insulinära (1895—1922)

Frauen	21
Männer	50
Kinder (= 20 Jahre und darunter)	10
	<hr/>
Zusammen	81

Während der Insulinära (1923—1943)

Frauen	35
Männer	40
Kinder (= 20 Jahre und darunter)	10
	<hr/>
Zusammen	85

Das ganze Diabetikermaterial beträgt also 166, darunter 146 Erwachsene.

In Abb. 1 und 2 ist die Verteilung des Materials auf Altersgruppen im präinsulinären und im Insulinzeitalter dargestellt. Des Vergleichs halber führe ich die Verteilung des Obduktionsmaterials des Pathologisch-anatomischen Instituts auf Altersklassen in den entsprechenden Zeitabschnitten an (dem Insulinzeitalter entspricht jedoch der Zeitabschnitt 1923—1940). Beim Vergleich der Abbildungen gewinnt man die Auffassung, dass in der Gruppe der alten Frauen in der Periode 1923—1943 relativ mehr Diabetespatientinnen obduziert worden sind als in der Periode 1895—1922. Ob dies auf die bekannte Zunahme des Diabetes ins besondere bei alten Frauen hindeutet (vgl. z. B. Joslin, 1940), ist schwer mit Sicherheit zu entscheiden.

Der überwiegend grösste Teil des Obduktionsmaterials vom Pathologisch-anatomischen Institut stammt aus den Universitätskliniken von Helsinki. Die Obduktionen sind im allgemeinen binnen 1—2 Tagen nach dem Tode ausgeführt worden. Vor der Obduktion wurden die Leichen in einem kühlen Keller aufbewahrt (seit 1943 in einem mit einer Kühleinrichtung versehenen Raum). Nach den Berichten zu schliessen sind die Obduktionstraditionen während der ganzen Zeitfolge in grossen Zügen unverändert geblieben. Ausgeführt wurden die Obduktionen von den Institutslehrern, häufig mit Unterstützung der studierenden Kandidaten der Medizin.

Das verfügbare Diabetiker-Obduktionsmaterial ist also nicht allzu gross, aber es ist eben das Material, das benutzt werden muss, wenn wir die pathologische Anatomie des Diabetes in Finnland während der vergangenen 50 Jahre studieren wollen. Darüber hinaus sind nämlich Diabetikerobduktionen nur in geringem Umfang in einigen Krankenhäusern ausgeführt worden.

Vergleichen wir wiederum die Grösse des Materials mit den Materialien ausländischer Forscher (Tab. III), so bemerken wir, dass, praktisch betrachtet, nur die Materialien von Simmonds und Warren grösser als das von mir benutzte Material sind.

Das Vergleichsmaterial. Die früheren Forscher haben sich im allgemeinen mit der Erwähnung des Umstandes begnügt, bei wievielen Obduzierten (oder in wieviel Prozent) irgendeine Organveränderung usw. vorgekommen ist. Sie haben offenbar den Zweck verfolgt, die Materialien der verschiedenen Forscher auf diese Art untereinander vergleichbar zu machen. Zwischen den ver-

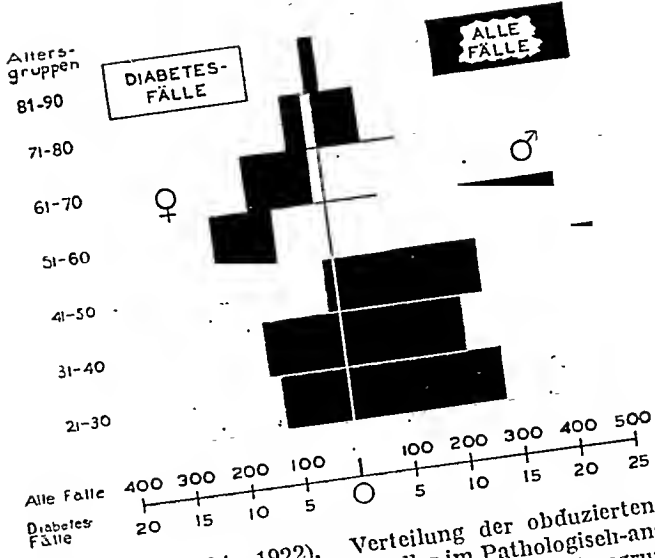


Abb. 1. Präinsulinära (1894—1922). Verteilung der obduzierten Diabetesfälle (weiss) auf Altersgruppen. Verteilung aller im Pathologisch-anatomischen Institut der Universität obduzierten Fälle (schwarz) auf Altersgruppen. Personen im Alter von 20 Jahren und darunter nicht einbegriffen.

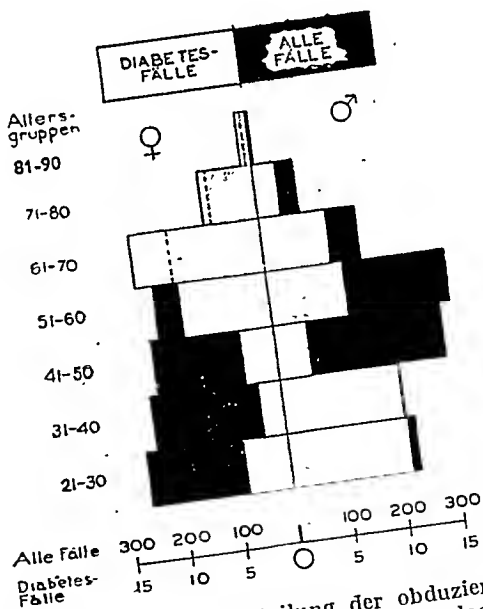


Abb. 2 Insulinära (1923—1943). Verteilung der obduzierten Diabetesfälle (weiss) auf Altersgruppen. Verteilung aller im Pathologisch-anatomischen Institut der Universität (in den Jahren 1923—1940) obduzierten Fälle (schwarz) auf Altersgruppen. Personen im Alter von 20 Jahren und darunter nicht einbegriffen.

Tabelle I.

Der Ernährungszustand der Diabetesfälle nach Altersgruppen.

	A l t e r, J a h r e								Zusammen
	1—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	
Sehr fett	—	—	—	—	1	2	—	2	5
Fett	1	—	1	1	3	5	7	—	18
Ziemlich fett ..	—	1	1	1	—	1	1	—	5
Mittelmässig ..	1	—	3	2	1	2	3	1	13
Ziemlich mager	—	2	8	5	2	3	1	—	21
Mager	—	4	5	12	1	5	5	1	33
Sehr mager ..	1	4	8	7	7	1	4	1	33
Zusammen	3	11	26	28	15	19	21	5	128

Tabelle II.

Der Ernährungszustand der Kontrollfälle nach Altersgruppen.

	A l t e r, J a h r e								Zusammen
	1—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	
Sehr fett	—	—	—	1	—	1	1	—	3
Fett	—	—	1	2	2	3	4	—	12
Ziemlich fett ..	—	1	2	4	2	3	2	1	15
Mittelmässig ..	—	2	6	3	1	2	1	—	15
Ziemlich mager	1	2	7	6	2	5	1	—	24
Mager	1	3	7	7	4	3	8	3	36
Sehr mager ..	1	3	3	5	4	2	4	1	23
Zusammen	3	11	26	28	15	19	21	5	128

schiedenen Materialien bestehen indessen stets Unterschiede, z.B. in der Verteilung der Patienten auf die verschiedenen Altersklassen, ein Umstand, der nicht einmal immer mitgeteilt ist. Hierzu können noch viele andere Unterschiede kommen, die man auf den ersten Blick gar nicht bemerkt. Ich hielt es deshalb für angebracht, aus dem Material des Pathologisch-anatomischen Institutes ein Kontrollmaterial auszuwählen, mit dem ich das Diabetesmaterial vergleichen könnte.

Das Kontrollmaterial wurde so eingesammelt, dass für jedes Jahr entsprechend jedem Diabetiker eine Person gleichen Geschlechtes und Alters ausgewählt wurde (in den älteren Alters-

klassen musste man hierbei bisweilen eine um ein Jahr ältere oder jüngere Person nehmen). Die Diagnose wurde in diesem Zusammenhang natürlich nicht berücksichtigt.

Ausserdem las ich in den betreffenden Krankenhäusern (die Diabetiker stammten in der Hauptsache aus der I. und II. Medizinischen Universitätsklinik) die Krankengeschichten eines jeden Patienten durch, was u. a. deswegen unerlässlich war, um zu sehen, welche von ihnen Komafälle gewesen waren, um die Todesursache sicherzustellen usw.

Der Ernährungszustand. Allgemein bekannt ist die grosse Bedeutung, die der Fettsucht seit der Zeit Allens für den Ausbruch des Diabetes beigemessen wird. In den Obduktionsberichten befanden sich keine Aufzeichnungen über das exakte Gewicht der zu Obduzierenden, in den meisten Fällen aber auf das Körpergewicht hindeutende Bemerkungen («fett», «ziemlich fett» usw.). Obgleich es sich hierbei um eine subjektive Schätzung handelt, ordnete ich die Fälle doch aufgrund dieser Vermerke in Gruppen, wobei ich gleichzeitig das Alter der Patienten in Betracht zog (Tab. I und II). Wie wir aus Tab. I ersehen, war nur ein auffallend kleiner Teil der Diabetiker fett beim Sterben. Ebenso wenig bestehen in der Verteilung der Gewichte zwischen den Diabetikern und dem Kontrollmaterial nennenswerte Unterschiede; denn von den Diabetikern waren alles in allem 28 fett, 13 mittelmässig und 87 mager, während die entsprechenden Zahlen im Kontrollmaterial 30, 15 und 83 lauten. Auch die Verteilung der Gewichte in den verschiedenen Altersgruppen er bietet keine charakteristischen Verschiedenheiten zwischen den beiden Materialien.

Vergleichshalber sei erwähnt, dass von den 40 Fällen Hansemanns (1894) 26 mager, 3 «mässig abgemagert» und 7 fett waren. In 4 Fällen fehlt der Vermerk über den Ernährungszustand. Die Zahlen sind also sehr ähnlich wie die von mir oben mitgeteilten.

Die Pankreasveränderungen.

Wenn es sich um den Diabetes handelt, erweckt die pathologische Anatomie des Pankreas besonderes Interesse.

Die älteren Ärzte haben den Diabetes als eine Blut-, Nieren- oder Darmkrankheit angesprochen. Im Jahre 1845 erfasste Bouchardat als erster den Zusammenhang des Pankreas mit dieser

Krankheit, nachdem er bei mehreren, wenngleich nicht bei allen an Diabetikern vorgenommenen Obduktionen eine Pankreasatrophie bemerkt hatte. Um seine Theorie zu beweisen, versuchte er experimentelle Pankreasexstirpationen auszuführen, aber die Versuchstiere überstanden in dem damaligen Entwicklungsstadium der Chirurgie keine so grosse Operation. Auch Lancereaux (1877) beobachtete in seinen »diabète-maigre«-Fällen regelmässig Pankreasveränderungen. Erst von Mering und Minkowski (1889) gelang es, bei Hunden durch die Pankreasexstirpation einen wirklichen Diabetes hervorzubringen, und sie bewiesen hierdurch den Zusammenhang zwischen der Krankheit und dem Pankreas.

Die erste umfangreichere Arbeit über die pathologische Anatomie des Pankreas (hauptsächlich vom makroskopischen Standpunkt) publizierte Hansemann (1894). Er beschrieb die »Granularatrophie« des Pankreas (die später gewöhnlich als Hansemannsche Atrophie bezeichnet wurde), bei der das Pankreas in der Regel schlaff und etwas dunkel gefärbt ist. Das ganze Organ ist verdünnt, die Drüsenläppchen sind klein. Das Binde- und das Fettgewebe der Umgebung setzen sich in das Pankreas fort, das hierdurch schwer herauszupräparieren ist. Das Stroma erfüllt die Zwischenräume zwischen den verkleinerten Drüsenläppchen mehr oder weniger genau und enthält stets an einigen Stellen frischere Wucherungen in Gestalt einer zelligen Infiltration. Mit dem passiven atrophischen Prozess ist also eine aktive interstitielle Entzündung verbunden. In stark kachektischen Zuständen konnte das Pankreas auch einigermassen atrophisiert sein, aber es war dann walzenförmig verschmälert. Das Fettgewebe der Umgebung war geschwunden, und das Organ liess sich leicht herauspräparieren. In der Publikation Hansemanns werden die Langerhansschen (1869) Inseln nicht erwähnt. Er war ja einer der Hauptanhänger der sog. azinären Theorie, nach welcher die Kontrolle des Kohlenhydratstoffwechsels im Pankreas ausserhalb der Inseln lokalisiert ist.

Um dieselbe Zeit richtete Dieckhoff (1894) als erster seine Aufmerksamkeit auf die Veränderungen in den Langerhansschen Inseln bei Diabetikern. Warren (1938) hält seine Ergebnisse wegen der unentwickelten Färbungsmethoden für unsicher.

Erst die Untersuchungsergebnisse von Ssobolew (1900, 1902) und Opie (1901) erwiesen, dass die Inseln in Diabetesfällen sehr

Tabelle III.

Das Vorkommen von Pankreasveränderungen in den Materialien der verschiedenen Autoren.

Jahr Verfasser	Gesamt- zahl der Fälle	Pan- kreas normal	Pankreasveränderungen					Bemerkungen
			Atro- phie	Zirrhose (Fibrose, Indura- tion)	Verfet- tung	Kon- kre- mente	Mal. Tumor	
1879 Lapierre	15		6			6	3	
1883 Windle....	39	65	38	5	11	3	3	Hämochroma- tose 1 Hämorrhagien 1
1884 Frerichs		28	10			1	1	Abszess 1 Hämorrhag. Pankreatit. 1
1888 Noltenius....	11	4		4		1		
1894 Seegen	30		13		1	1		
1894 Hansemann..	54	8	36	3				„Komplizierter Fall“ 1 Sonstige Veränder. 15
1894 Hansemann Literatur	72		38			14	5	
1900 Naunyn	40	20	4	4	2	1		
1901 Weichselbaum u. Stangl	18	1	17					
1909 Halász	44	5	25					
1910 Weichselbaum	183		8	3	32	1	1	Eitrige Entzünd. 1 Bronzediabetes 2
1912 Simmonds....	150	58	45	12	32	4		
1921 Simmonds....	300	Die Verhältnisse wie im Vorigen						
1933 Herxheimer ..	162	38		105				Unsichere 19
1934 Lundberg ..	91		29	9	24	4	2	
1938 Warren	527	127 ¹	74	269	145	3	10	Pankreatitis ac. 5 Abszess 4 Amyloid 2

¹ Histologisch

oft verändert waren. Gleichzeitig konnten auch Veränderungen im azinären Gewebe vorliegen, aber dieselben konnten auch fehlen. In den Fällen dagegen, wo kein Diabetes bestand, obwohl das Pankreasgewebe z.B. infolge eines Karzinoms weitgehend zerstört war, waren die Inseln normal.

Nachdem eine emsige und mannigfaltige Forschungsarbeit zur Entdeckung des Insulins (Banting und Best, 1922) geführt hatte, hatte die Frage nach der Bedeutung des Pankreas für den Kohlenhydratstoffwechsel ihre grosse Entscheidung gefunden.

Über das Vorkommen von Pankreasveränderungen bei Diabetikern existiert eine umfangreiche Literatur. In Tab. III habe ich aus dem Schrifttum die Angaben über das Vorkommen von Pankreasveränderungen bei Diabetikerobildungen in den Materialien der verschiedenen Forscher zusammengestellt. Wie man aus der Tabelle ersieht, ist das Pankreas in einem erheblichen Teil der Fälle als normal betrachtet worden. Häufig hat sich das Urteil offenbar nur auf die makroskopische Beobachtung gegründet.

Bei dem von mir benutzten Material war das Hauptaugenmerk auf die Grösse, Farbe und Konsistenz des Pankreas sowie auf das eventuelle Vorkommen einer Zirrhose, Verfettung und maligner Tumoren gerichtet worden. Mikroskopische Untersuchungen wurden verhältnismässig wenig ausgeführt.

Das Pankreas gehört zu den Organen, an denen sich die postmortalen Veränderungen am schnellsten bemerkbar machen. Deswegen und in Anbetracht dessen, dass das Material nicht immer gleich lange nach dem Tode obduziert worden ist, habe ich geglaubt, den auf die Farbe und Konsistenz des Organs bezüglichen Äusserungen kein allzu grosses Gewicht beimessen zu können.

Die Pankreasatrophie. Das Vorkommen einer Pankreasatrophie beim Diabetes spiegelt sich in den Wägungsergebnissen des Organs wider. Es ist jedoch zu beachten, dass eine starke Vermehrung des Bindegewebes oder Fettes auch das Gewicht eines atrophischen Organs beträchtlich erhöhen.

Hansemann (1894) hielt dafür, dass das normale Gewicht des Pankreas beim Manne ca 100 g beträgt und hielt deshalb z.B. ein Pankreas im Gewicht von 70 g schon für deutlich atrophisch. In seiner späteren Publikation teilt von Hansemann (1912) mit, dass das Normalgewicht der Bauchspeicheldrüse zwischen 70 und 180 g schwankt.

Nach Dieckhoff (1894) beläuft sich das mittlere Gewicht der Drüse auf 80 g. Bei Halász (1909) variieren die Gewichte von 90—105 g. Vierordt (1906) berechnet, dass die Bauchspeicheldrüse beim erwachsenen Manne durchschnittlich 0.15 % des Körpergewichts ausmacht.

Über das Pankreasgewicht finden sich in der älteren Literatur auch mehrere andere Einzelangaben (vgl. z.B. die von Rössle, 1921, Roessle und Roulet, 1932, Sklawunos, 1922 und Gruber, 1929 vorgelegten Zusammenfassungen). Dem Altersfaktor hat von den früheren Forschern Wideroe (1910) Beachtung geschenkt, dessen Ergebnisse aber, wie Rössle (1921) bemerkt, für die Jugendjahre zu hoch und für die reifen Jahre zu niedrig sind.

Rössle (1921) gibt als Durchschnittsgewicht des Pankreas bei seinem Soldatenmaterial (400 Fälle zwischen 18 und 45 Jahren) 88 g an. Nachdem er alle protrahierten Krankheitsfälle, bei denen man eine durch die Krankheit bedingte Atrophie annehmen konnte, sorgfältig ausgesondert hatte, blieben ihm 79 Fälle mit einem Durchschnittsgewicht von 91.6 g. In derselben Publikation stellt Rössle das Material Wilhelm Müllers (352 Obduzierte männlichen und 282 weiblichen Geschlechts) dar, aus dem hervorgeht, dass das Pankreasgewicht von Alter und Geschlecht abhängig ist. Es steigt zunächst steil, später sanft an und erreicht seinen höchsten Punkt im Alter von 35 Jahren, um von da ab wieder langsam abzufallen. Zur Beleuchtung der Sache greife ich einige Zahlen aus Müllers Material heraus (die Zahlen sind zu vollen Grammen abgerundet):

Alter	Pankreasgewicht	
	Männer	Frauen
21—25	70	59
26—30	76	64
31—40	76	69
41—50	72	67
51—60	67	59
61—70	67	55
71—80	61	52

Nach Krieger (1921) hat man als mittleres Gewicht des Pankreas erwachsener Männer 97.8—99.6 g erhalten. Warren (1938) teilt mit, dass die Gewichte zwischen 60 und 160 g variieren und das Gewicht durchschnittlich 95 g beträgt.

Von den späteren Forschern erwähne ich noch Uotila (1942), der in seiner kürzlich erschienenen Untersuchung über die Organgewichte bei Finnen in bezug auf die Bauchspeicheldrüse

zu ähnlichen, wenngleich etwas höheren Resultaten als die oben dargestellten gekommen ist. Als Pankreasgewicht für ausgewachsene (25—50-jährige) finnische Männer erhielt er durchschnittlich 79.7 g und für Frauen (20—50-jährige) 68.1 g.

In diesem Zusammenhang sei erwähnt, dass die Bauchspeicheldrüse nach Krieger (1920) bei der Inanition, Geschwulstkachexie und Tuberkulose bis zu einem Drittel ihres Gewichts einbüßen kann.

Über das Pankreasgewicht bei Diabetikern liegen im Schrifttum ebenfalls Angaben vor.

Von den insgesamt 40 Fällen Hansemanns (1894) wurde das Pankreas nur in 9 Fällen gewogen, wobei sich folgende Gewichte ergaben:

einmal	97 g
einmal	65 »
fünfmal	50 »
einmal	35 » und
einmal	24 »

Von den 7 Fällen Dieckhoffs (1894) waren nur 2 gewogen (30 und 39 g).

Bei Halász (1909) schwankte das Pankreasgewicht von 25 Diabetikern zwischen 19 und 85 g und von 3 Diabetikern zwischen 90 und 105 g. Nach ihm ist das Pankreas bei schwerem Diabetes und jungen Personen gewöhnlich klein, die Hälfte des »Normalgewichts«. Das niedrigste Gewicht findet man jedoch bei alten Menschen, deren Pankreas zum grössten Teil aus bindegewebigen Strängen besteht.

In seiner gründlichen Publikation teilt Weichselbaum (1910) Angaben über 183 Diabetesfälle mit; das Pankreas war jedoch nicht in allen Fällen gewogen worden. Um die Ergebnisse Weichselbaums mit meinen eigenen vergleichen zu können¹, habe ich seine Ergebnisse nach den gleichen Grundsätzen wie meine eigenen (Tab. IV und V) in Tabellenform (Tab. VI) geordnet. Das Maximum der Fälle liegt bei seinem Material in der Gewichtsgruppe 41—50 g. Weichselbaum macht darauf aufmerksam, dass die grössten Gewichtsvermindierungen bei Erwachsenen unter

¹ Der Altersaufbau von Weichselbaums Material ist nicht ganz derselbe wie in meinem Material, was bei der Ausstellung von Vergleichen zu berücksichtigen ist.

Tabelle IV.

Die Verteilung der Pankreasgewichte bei den Diabetikern in den verschiedenen Altersgruppen.

Pankreas- gewicht g	A l t e r, J a h r e								Zusam- men
	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	
11—20	1	—	1	1	—	1	—	—	4
21—30	—	1	7	1	—	1	1	—	11
31—40	—	2	3	3	—	2	1	—	11
41—50	—	4	5	3	3	1	1	1	18
51—60	—	1	1	2	1	4	3	2	14
61—70	—	1	2	2	1	1	3	2	12
71—80	—	—	2	1	1	2	3	—	9
81—90	—	—	—	—	1	—	1	1	3
91—100	—	—	—	1	—	2	2	—	5
101—110	—	—	—	—	—	—	—	—	—
111—120	—	—	1	—	—	1	1	—	3
121—130	—	—	1	—	—	—	—	—	1
131—140	—	—	—	—	—	1	1	—	2
141—150	—	—	—	—	—	2	—	—	2
175	—	—	1	—	—	—	—	—	1
Zusammen	1	9	24	14	7	18	17	6	96

50 Jahren beobachtet werden, indem die Gewichte bei 20—40-jährigen am gewöhnlichsten unter 45 g betragen. Das niedrigste Pankreasgewicht eines Erwachsenen belief sich auf 28 g (32-jährige Frau mit Pneumonie und Koma). Das höchste Gewicht betrug 155 g. Es handelte sich um einen 55-jährigen Mann mit Akromegaliasymptomen, aber ohne makroskopische Veränderungen der Hypophyse. Ein relativ hohes Pankreasgewicht, 125 g, lag in einem andern Akromegalfall, bei einem 26-jährigen Weibe mit malignem Hypophysentumor vor. Bei den übrigen hohen Pankreasgewichten handelte es sich um Lipomatose oder Krebsknoten.

Auf die niedrigeren Pankreasgewichte jüngerer Diabetiker weist auch Simmonds (1921) hin.

Bei 10 jungen Diabetikern von Kraus (1923) schwankte das Gewicht zwischen 19 und 62 g (durchschnittlich 42 g). Bei 9 Diabetikern im Alter von 49—70 Jahren betrugen die Gewichte 45—115 g (durchschnittlich 80,3 g).

Tabelle V.

Die Verteilung der Pankreasgewichte bei den Kontrollfällen in den verschiedenen Altersgruppen.

Pankreas- gewicht g	A l t e r, J a h r e								Zusam- men-
	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	
11—20	—	—	—	—	—	—	—	—	—
21—30	1	—	—	—	—	—	—	—	1
31—40	—	1	—	—	—	—	—	—	1
41—50	—	3	4	3	—	—	1	—	11
51—60	—	—	—	—	1	3	2	2	8
61—70	—	2	3	—	2	5	3	1	16
71—80	—	3	4	3	3	2	2	1	18
81—90	—	—	5	3	1	2	—	1	12
91—100	—	—	2	2	—	1	4	—	9
101—110	—	—	4	1	—	1	2	1	9
111—120	—	—	1	—	—	1	1	—	3
121—130	—	—	1	—	—	—	—	—	1
131—140	—	—	—	—	—	1	2	—	3
141—150	—	—	—	2	—	—	—	—	2
151—160	—	—	—	—	—	—	—	—	—
161—170	—	—	—	—	—	1	—	—	1
250	—	—	—	—	—	1	—	—	1
Zusammen	1	9	24	14	7	18	17	6	96

In dem grossen Material Warrens (1938), wo das Pankreas in 449 Fällen gewogen war, verteilten sich die Gewichte folgendermassen:

In 74 Fällen deutlich klein, unter 50 g
 „ 301 „ normal, 50—100 g
 „ 74 „ gross, über 100 g.

Aus Tab. IV erhellt die Verteilung der Pankreasgewichte bei den Diabetikern des vorliegenden Materials in den verschiedenen Altersgruppen. Weil das Pankreas von anderen als Diabetikerleichen in früheren Jahren oft ungewogen geblieben ist, sind aus dem Material auch solche Diabetiker ausgesiebt, bei deren Kontrollfällen das Pankreas nicht gewogen worden war. Auf diese Art sind 96 Fälle übrig geblieben. Aus Tab. V ersieht man die entsprechende Verteilung der Kontrollfälle.

Wie wir sehen, ist die Verteilung in den beiden Tabellen verschied-

Tabelle VI.

Die Verteilung der Pankreasgewichte bei den Diabetikern in den verschiedenen Altersgruppen (Weichselbaums Material, das ich hier nach denselben Prinzipien wie mein eigenes tabellarisch darstelle).

Pankreas- gewicht g	A l t e r, J a h r e								Zusam- men
	1—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	
11—20	2	—	—	—	—	—	—	—	2
21—30	—	6	2	1	—	—	—	—	9
31—40	—	7	2	6	2	3	—	—	20
41—50	—	4	12	8	6	6	3	1	40
51—60	—	—	9	5	5	1	2	—	22
61—70	—	1	2	6	6	9	9	1	34
71—80	—	1	1	1	3	4	2	1	13
81—90	—	—	—	1	1	3	3	—	8
91—100	—	—	1	1	1	1	2	—	6
101—110	—	—	—	—	1	1	2	—	4
111—120	—	—	—	—	1	1	—	2	4
121—130	—	—	1	—	—	2	—	—	3
131—140	—	—	—	—	1	2	—	1	4
141—150	—	—	—	—	1	—	—	—	1
151—160	—	—	—	—	—	1	1	—	2
Zusammen	2	19	30	29	28	34	24	6	172

den. Das Maximum der Fälle in der Diabetikertabelle liegt bei 41—50 g, das Maximum des Kontrollmaterials wiederum bei 71—80 g. Die letzterwähnte Zahl entspricht dem von Uotila (1942) angegebenen mittleren Pankreasgewicht (wegen der Kleinheit des Materials habe ich Männer und Frauen nicht auf getrennte Tabellen verteilt). Bei näherer Betrachtung der Tabellen IV und V bemerken wir zudem, wenn wir nur die Erwachsenen (21 Jahre und darüber) ins Auge fassen, dass in die Gewichtsklassen 40 g und darunter insgesamt 22 Diabetiker eingehen, von den Kontrollfällen dagegen kein einziger. Das Pankreas im Gewicht von 250 g wurde unter den Kontrollfällen bei einem 52-jährigen Mann mit Hypophysentumor und Akromegalie angetroffen.

Aus Tab. IV erselen wir ferner, dass die maximale Menge der Fälle bei den Diabetikern in den jüngeren Altersklassen auf niedrigere Gewichtsklassen als in den älteren zu entfallen scheint. Auf diesen Umstand hat schon Weichselbaum (1910) hingewiesen (vgl. Tab. VI).

Um die in den Pankreasgewichten bei den Diabetikern und in den Kontrollfällen herrschenden Unterschiede zu veranschaulichen, habe ich die in Abb. 3 wiedergegebenen Kurven gezeichnet. Als Abszisse sind die Pankreasgewichte und als Ordinate die der jeweiligen Gewichtsgruppe entsprechende Anzahl Fälle verwendet worden. Beim Zeichnen der Kurven habe ich aus den Tabellen IV und V lediglich die 21-jährigen und älteren Fälle berücksichtigt.

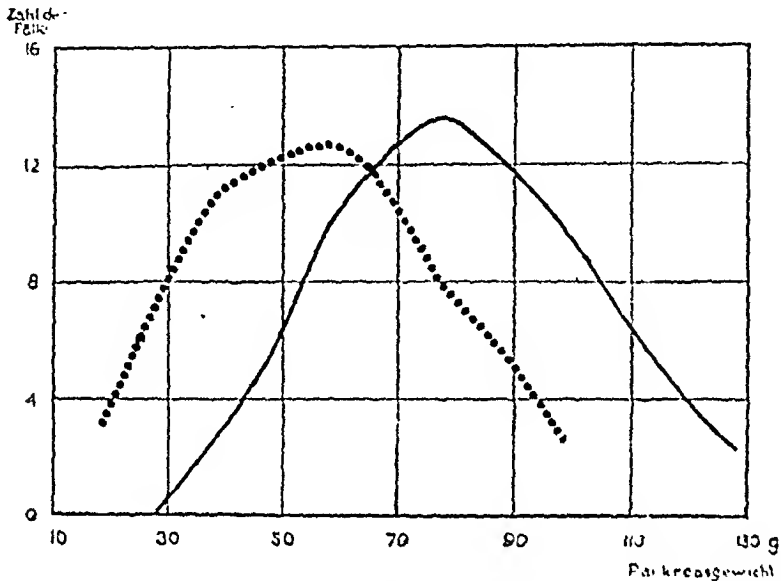


Abb. 3. Verteilung der Pankreasgewichte Erwachsener auf verschiedene Gewichtsgruppen.

..... Bauchspeicheldrüsen der Diabetiker
 ————— Bauchspeicheldrüsen der Kontrollfälle.

In dem benutzten Material sind die Pankreasgewichte sehr oft nur mit 10 g Genauigkeit angegeben. Anstatt der von mir verwendeten Gewichtsgruppen 11—20, 21—30, 31—40 g usw. wäre es zweifellos richtiger gewesen, eine Einteilungsmethode zu gebrauchen (z. B. 15—24, 25—34, 35—44 g usw.), bei welcher der grösste Teil der Fälle (nämlich alle vollen Zehner) in die Mitte jeder Gruppe gelangt wären. Die ersterwähnte Einteilungsmethode scheint jedoch allgemeiner im medizinischen Schrifttum im Gebrauch zu sein, sodass ich es für zweckmässiger gehalten habe, sie beizubehalten. Bei der Ausführung von Mittelwertberechnungen kam ich zu dem Ergebnis, dass das Zentrum jeder Gewichtsgruppe bei der auf 8 endigenden Gewichtszahl liegt (also z.B. in der Gruppe 31—40 g bei 38 g). Deswegen wurden die Ordinatenwerte beim Zeichnen der Kurven in Abb. 3 auf den erwähnten Abszissenpunkten verzeichnet. Zum Ausgleich der in den Werten der Tabellen IV und V auftretenden Schwankungen bin ich so vorgegangen, dass als Ordinatenwert in jedem Punkte das Mittel von 3 aufeinanderfolgenden Werten angenommen wurde.

Aus Abb. 3 erhellt, dass die ansteigenden Teile der beiden Kurven und andererseits die abfallenden Teile annähernd parallel verlaufen, wobei die Differenz zwischen den Diabetikern und den Kontrollfällen durchweg etwa 22—26 g beträgt.

Wie oben erwähnt, sind in Tab. IV deshalb nicht alle Diabetesfälle behandelt worden, weil das Pankreas bei dem entsprechenden Kontrollfall nicht gewogen war. Diese Fälle belaufen sich alles in allem auf 27 (über 21-jährige), deren Pankreasgewichte sich folgendermassen auf die verschiedenen Gewichtgruppen verteilen:

1—10 g.....	1 Fall
21—30 ».....	3 Fälle
31—40 ».....	5 »
41—50 ».....	4 »
51—60 ».....	3 »
61—70 ».....	2 »
71—80 ».....	3 »
81—90 ».....	2 »
91—100 ».....	1 Fall
111—120 ».....	2 Fälle
141—150 ».....	1 Fall

In 19 ungewogenen Fällen ist ausserdem eine Pankreasatrophie erwähnt. Von allen erwachsenen Diabetesfällen, in denen das Pankreas gewogen war, fand sich in 57 eine Aufzeichnung über Atrophie. Das grösste Pankreas, das als atrophisch erwähnt war, wog 80 g. Hierbei waren die Lobuli kleiner als gewöhnlich und das interstitielle Bindegewebe war vermehrt. Von den gewogenen Bauchspeicheldrüsen wogen insgesamt 53 Stück 50 g und darunter, eine Zahl, die der oben erwähnten Zahl 57 ungefähr entspricht. In den Kontrollfällen fand sich kein einziges Mal eine Aufzeichnung über Atrophie.

Beim Betrachten der Pankreasgewichte von Diabetikern kommt man auf den Gedanken, wie klein dasselbe bei einem erwachsenen Diabetiker sein kann. In den Materialien der verschiedenen Autoren werden folgende Mindestgewichte des Pankreas erwähnt: Dieckhoff (1894) 30 g, Weichselbaum (1910) 28 g, Halász (1909) 19 g und Kraus (1923) 19 g. Ausserdem sind im Schrifttum mehrere Fälle beschrieben, in denen das Pankreasgewebe völlig oder beinahe vollständig verschwunden war. Solche gibt es sowohl im Zusammenhang mit Pankreassteinen als ohne diese. Derartige

Tabelle VII.

Erwachsene Diabetiker mit einem Pankreasgewicht von 30 g oder darunter.

Geschlecht	Alter, Jahre	Gewicht des Pankreas, g	Dauer der Zuckerkrankheit, Jahre	Todesursache
männl. ..	21	30	3	Tub. pulm.
» ..	30	30	4	Coma, Tonsillit. purulenta
weibl. ..	23	30	7	Tub. pulm.
» ..	50	30	0.3	Coma
männl. ..	31	30	3.5	Tub. pulm.
» ..	21	30	1	Coma, Otit. med. suppurat.
weibl. ..	27	30	?	Coma
männl. ..	27	28	1.1	Coma
» ..	24	28	0.15	Bronchopneumonia
» ..	22	27	?	Coma
» ..	27	26.5	2	Coma, Bronchopneumonia
weibl. ..	59	25	7.5	Coma, Bronchopneumonia
» ..	65	25	?	Bronchopneumonia
» ..	26	23	?	Coma, Bronchopneumonia
männl. ..	38	20	3	Tub. pulm. et reg. var.
» ..	24	18	4	Nephritis ascend. suppurat.
weibl. ..	55	15	3.7	Coma, Pneumonia lobaris
männl. ..	38	9	1.4	Tub. pulm.

Fälle werden u. a. von Seegen (1870), Hansemann (1894), Dieckhoff (1894), Rössle (1921) und Kraus (1929) referiert.

Weil in das von mir benutzte Material zahlreiche kleine Bauchspeicheldrüsen eingingen, gebe ich in Tab. VII eine Zusammenfassung der Fälle wieder, in denen das Pankreasgewicht bei 21-jährigen oder älteren Personen 30 g oder darunter betrug. Aus der Tabelle ersehen wir, dass die Todesursache bei diesen Patienten in 10 Fällen Coma diabeticum, in 5 Fällen Tub. pulmonum und in 3 Fällen eine andere gewesen ist. Das mittlere Alter scheint bei den Frauen (ca 44 Jahre) höher gewesen zu sein als bei den Männern (ca 28 Jahre). Beim Vergleich der in Tab. VII dargestellten Fälle mit den Obduktionsergebnissen der anderen Diabetiker wurde kein gemeinsamer Zug bemerkt, der für diese Gruppe besonders charakteristisch gewesen wäre.

Das niedrigste Pankreasgewicht bei Erwachsenen in den Kontrollfällen betrug 45 g, das zweimal auftrat, nämlich bei einem 25-jährigen Weibe und einem 21-jährigen Manne.

Die Pankreaszirrhose. Bei einer Vermehrung des Bindegewebes wird das Pankreas derber. Bei einem ganz frischen Obduktionsmaterial ist dies vielleicht nicht so augenfällig wie bei einem etwas älteren, wo die »derbe Konsistenz eines bereits autolytisch veränderten Pankreas auf eine stärkere Wucherung des Bindegewebes mit ziemlicher Sicherheit schliessen lässt» (Kraus, 1929)¹. Dem Beispiel Herxheimers (1906, 1920) folgend, spricht man meistens von einer Pankreaszirrhose.

Warren (1938) spricht von einer Fibrose als der einfachsten und gewöhnlichsten Pankreasveränderung. Die Bindegewebswucherung ist in der Hauptsache vom interazinären Typus. Eine deutliche Beziehung zwischen der Schädigung der Inseln und der interazinären Fibrose besteht nicht. Von den 269 Fibrosefällen Warrens war diese Veränderung in 113 Fällen schwach, in 116 Fällen mittelstark und in 40 Fällen stark ausgeprägt.

In meinem Material finden sich bei Diabetikern auf eine Pankreaszirrhose hindeutende Vermerke, wie folgt:

In der Altersgruppe	11—20 Jahre	3 mal
» » »	21—30	» 2 »
» » »	31—40	» 7 »
» » »	41—50	» 6 »
» » »	51—60	» 4 »
» » »	61—70	» 5 »
» » »	71—80	» 3 »

In dem Kontrollmaterial lagen keine auf eine Zirrhose hindeutenden Aufzeichnungen vor.

Die Pankreasverfettung. Bisweilen ist bei alten Diabetikern (oft in Verbindung mit einer Vermehrung des Bindegewebes) eine mehr oder weniger starke Fettgewebswucherung zu beobachten. Hierbei kann das Gewicht des Organs natürlich erhöht sein. Die Verfettung der Bauchspeicheldrüse kann ein Symptom von allgemeiner Fettsucht darstellen.

In meinem Material wurde eine Verfettung beobachtet, wie folgt:

In der Altersgruppe	51—60 Jahre	4 mal
»	61—70	» 2 »

¹ Nach von Hansemann (1912) hängt die Härte des Pankreas vorwiegend von seinem Funktionsgrad ab, sodass eine arbeitende Drüse hart, eine im Ruhezustand befindliche weich mit allen Übergangsformen ist.

In dem Kontrollmaterial wird die Verfettung einmal in der Altersgruppe 51—60 Jahre erwähnt.

Die Pankreassteine. Zu den Eigentümlichkeiten des Pankreas gehört das Vorkommen von Konkrementen, Sialolithen, was schon lange bekannt ist (Graaf, 1667). Die Pankreassteine treten oft in mehreren Exemplaren in den Ausführungsgängen, vorwiegend nahe der Duodenalmündung auf. Sie liegen frei im Lumen oder sind an der Wand fixiert. Ihre Grösse variiert von der Grösse eines Hanfsamens bis zu der einer grossen Kirsche. Ihrer Form nach sind sie kugelig oder ovoid. Die Oberfläche kann glatt oder rauh, ja sogar dendritisch verzweigt sein. Die Farbe ist weiss, grau oder gelblich, selten dunkler. Die Steine enthalten zumeist Kalziumkarbonat oder -phosphat, ein Umstand, der es bedingt, dass man sie oft intra vitam auf dem Röntgenbilde erkennen kann (Lazarus, 1904, Morrison und Bogan, 1928). Ausserdem kommen u.a. Cholesterin und Aminosäuren darin vor. Nach Oser (1898) treten Steine bei Männern 4 mal so oft als bei Frauen auf (die Statistik bezieht sich auf nur etwa 30 Fälle) und nach Lazarus (1904) etwa 5 mal so oft (47 Männer, 10 Frauen). Zusammenfassungen über das Vorkommen von Pankreassteinen haben Oser (1898), Lazarus (1904) und Faust (1935) publiziert. Aus Finnland hat von Bonsdorff (1930) einen Fall von Pankreasstein veröffentlicht. Es handelte sich um einen 60-jährigen Mann, der Alkoholiker war. Diabetes lag nicht vor. Bei der Obduktion wurden ausser einer Leberzirrhose zahlreiche erbsengrosse und kleinere, weisse oder gelbliche harte Konkreme im Drüsengewebe des Pankreas festgestellt.

Cawley publizierte i.J. 1788 einen Fall, wo das Pankreas eines an Diabetes gestorbenen Patienten voller Steine und das Pankreasgewebe hochgradig verändert war. Die Steine verursachen auch dann, wenn sie den Ausführungsgang verstopfen, ein Atrophieren des Pankreas, das anfänglich vorwiegend das azinäre, später auch das insuläre Gewebe betrifft. Man erinnere sich in diesem Zusammenhang z.B. der Unterbindungsversuche des Ductus (Ssobolew, 1900, 1902), bei denen ebenfalls eine Pankreasatrophie erzielt wurde. Die Unterbindungsversuche wiederum brachten Banting auf die Idee, zur Herstellung des inneren Pankreassekrets eine Drüse zu verwenden, in der man das azinäre Gewebe zum Atrophieren gebracht hatte (Banting und Best, 1922).

Anderen Forschern zufolge sollten die Steine in erster Linie sekundäre, auf Entzündungen des Pankreas zurückzuführende Erscheinungen sein.

Pankreassteinfälle bei Diabetikern haben u.a. veröffentlicht: von Recklinghausen (1864), Windle (1883, 3 Fälle), Frerichs (1894), Noltenius (1888), Freyhan (1893, 2 Fälle), Rowland (1893), Fleiner (1894), Lichtheim (1894), Naunyn (1900), Weichselbaum (1910), Simmonds (1912, 4 Fälle), Gross (1921), Möckel (1926, 2 Fälle), Wilder (1926, 3 Fälle unter 55 Obduktionen), Warren (1938, 3 Fälle unter 527 Obduktionen) und Joslin (1940).

In den 40 eigenen Fällen Hansemanns (1894) kam kein einziger Pankreasstein vor. Unter den von ihm aus der Literatur herausgelesenen 72 Diabetesfällen dagegen befanden sich volle 14 Steinfälle. Zusammenfassungen über das Vorkommen von Pankreassteinen bei Diabetikern haben ausserdem Oser (1898), Lazarus (1904) und Kraus (1929) mitgeteilt.

Unter den Diabetesfällen des Verfassers wurde ein Pankreassteinfall, nämlich aus dem Jahre 1911 angetroffen. Die Patientin war eine 32-jährige Kellnerin, die aus Schweden stammte. Zweijährige Diabetesanamnese. Hauptsymptome starker Durst und Abmagerung. Etwas Haarausfall und Übelkeit. Exitus im Zusammenhang mit einer Erysipelasinfection. Bei der Obduktion wurde ein Pankreas im Gewicht von 40 g festgestellt, dessen Schnittfläche bindegewebig war. Das Drüsengewebe schien verschwunden zu sein. Im Innern des Pankreas eine grosse Menge verschieden grosser, weisser Steine mit rauher Oberfläche.

Das Pankreaskarzinom. Im allgemeinen ist man der Ansicht, dass das Pankreaskarzinom relativ selten die Ursache eines Diabetes bildet, weil gewöhnlich so viel intaktes Drüsengewebe erhalten ist, dass die Insulinsekretion fort dauern kann¹ (Kraus, 1929). So wurde ja in den 107 Pankreaskarzinomfällen von Germershausens (1904) nur 4 mal Zucker im Harn nachgewiesen. Ob der Urin in sämtlichen Fällen sorgfältig untersucht worden ist, geht nicht aus seiner Tabelle hervor, in der sich nur einmal der Vermerk »kein« findet.

Nach McKittrick und Root (1928) wiederum waren etwa ein Drittel aller malignen Tumoren bei Diabetikern Pankreaskarzinome (Totalanzahl der malignen Fälle 37).

¹ Das insuläre Gewebe kann sich, auch wenn es von Tumorgewebe umgeben ist, einigermaßen intakt erhalten (Marble, 1940).

Bei der Untersuchung von 10,000 Diabetikern fand Marble (1934) 256 maligne Tumoren, von denen 33 (= 13 %) primäre Pankreaskarzinome waren. Später beschreibt Marble (1940) noch 101 maligne Tumoren bei Diabetikern, darunter 12 (= 12 %) Pankreaskarzinome. Bei Nicht-Diabetikern ist die Zahl der Pankreaskarzinome in den Vereinigten Staaten bedeutend geringer, 2.5—4.8 % der anderen Karzinome.

In Warrens (1938) Material (527 Diabetiker) gingen 10 Pankreaskarzinome (= 21 % aller malignen Tumoren) ein.

Wenn das Karzinom im Pankreaskopf gelegen ist und den Ductus verstopft, kann die Folge hiervon genau wie in den Steinfällen und bei den Ligaturfällen eine Erweiterung des Ductus und ein Atrophieren des Pankreasgewebes sein. Falls die Atrophie so stark ist, dass sie sich auch auf die Inseln erstreckt, die resistenter sind, so folgt hieraus ein Diabetes. Zwei derartige Fälle hat Burkhardt (1936) publiziert.

Im Material des Verfassers kam bei Diabetikern zweimal ein Pankreaskarzinom vor. Der eine war ein 29-jähriger Mann. Weil die Krankengeschichte verloren gegangen war, konnte ich keine genaueren Angaben über den Verlauf seiner Krankheit bekommen. Bei der Obduktion wurde im Pankreaskopf ein kinderfaustgrosser knolliger Tumor gefunden, dessen Schnittfläche von grau-weißen, unscharf begrenzten Massen sowie weichen, zerfallenden, blauroten, haselnussgrossen Bezirken gebildet wurde. Der Pankreasschwanz war atrophisch, der Ausführungsgang auf Fingerdicke erweitert. Es handelte sich offenbar um ein primäres Pankreaskarzinom, das, im Caput gelegen, den Ductus verstopft sowie dessen Erweiterung und die Pankreasatrophie verursacht hatte. Der Tumor war augenscheinlich in diesem Fall an dem Diabetes schuld. Der zweite Fall betraf einen 48-jährigen Mann mit einjähriger Diabetesanamnese. Bei der Obduktion wurde ein Pyloruskarzinom angetroffen, das auch das Pankreas infiltrierte Metastasen fanden sich zumal in den Lymphdrüsen des Magens.

Der erstere der von mir beschriebenen Fälle war also verhältnismässig jung, 29 Jahre. Von Germershausen (1904) hat darauf aufmerksam gemacht, dass das Pankreaskarzinom oft bei sehr jungen Personen, ja sogar bei Neugeborenen vorkommt.

In den Kontrollfällen wurden 6 mal karzinomatöse Veränderungen des Pankreas festgestellt.

Die Syphilis. Früher wurde allgemein angenommen, dass der Syphilis als einem ätiologischen Faktor des Diabetes wichtige Bedeutung zukäme (vgl. z. B. Oser, 1898). Auf einen ablehnenden Standpunkt stellte sich u.a. Herxheimer (1907). Unter den 300 Diabetesobduktionen Simmonds' (1921) befanden sich 20 Fälle, die eine Syphilis gehabt hatten. Die durch die Syphilis bedingten Pankreasveränderungen waren jedoch offenbar nur in 3 von diesen Fällen an dem Diabetes schuld gewesen. Die betreffenden Pankreasdrüsen waren atrophisch (26—36 g), fibrös, mit der Umgebung verwachsen und wiesen nur Reste von Drüsengewebe auf. Warren (1938) ist ebenfalls der Meinung, dass die syphilitischen Veränderungen des Pankreas nur selten die Ursache eines Diabetes bilden.

In dem Material des Verfassers war eine Syphilis bei 5 Diabetikern klinisch, serologisch oder gelegentlich der Obduktion konstatiert worden. In keinem einzigen Fall lagen auf die Syphilis hindeutende spezifische Veränderungen im Pankreas vor.

Unter den Kontrollfällen belief sich die Zahl der Syphilitiker auf 7.

Die Arteriosklerose des Pankreas. In Warrens (1938) Fällen bestand nur bei 5 % eine starke Sklerose der Pankreasgefäße, sodass man dieselbe wohl nicht als allzu wichtiges ätiologisches Moment betrachten kann, obwohl sich ihre Bedeutung andererseits nicht völlig bestreiten lässt. Nach Umber (1939) kann die Sklerose der Pankreasgefäße den Ausbruch eines Diabetes veranlassen, wenn es sich um erbbedingte Minderwertigkeit des Inselapparates handelt.

In dem von mir untersuchten Material ist dem eventuellen Vorkommen einer Arteriosklerose in den Pankreasgefäßen keine Beachtung geschenkt worden.

Sonstige Pankreasveränderungen. Die Tuberkulose im Pankreas ist nach Kaufmann (1931) selten; man hat die Drüse sogar für immun gegen Tuberkulose gehalten. Man kann indessen miliare Tuberkel im Pankreas beobachten, deren Folge ein Diabetes sein kann. Kraus (1929) hält das Vorkommen von Tuberkulose als Ursache eines Diabetes für fraglich.

In das von mir benutzte Material ging ein 16-jähriger Jüngling mit Pankreastuberkulose ein. Der Patient hatte 8 Monate an Müdigkeit und Übelkeit gelitten. Später stellten sich Stiche in der Brust, Husten, blutiger Auswurf und Schweisse ein. Schliesslich kontinuierlicher Burchfall und rasche Verschlechterung. Im Krankenhaus wurde Zucker im Harn nachgewiesen. Die Diabetesdiagnose war nicht ganz sicher. Bei der Obduktion wurden Lungentuberkulose III. Grades, tuberkulöse Geschwüre im Larynx und Darm sowie Miliartuberkel der Pia mater festgestellt. Der Kopfteil des Pankreas war schlaffer, seine Venen erweitert und das Parenchym stellenweise mit Blut imbibiert. Stellenweise bläulichweisse miliare Eruptionen. Pankreas sonst normal.

Die *a k u t e P a n k r e a t i t i s* kann zu einem Diabetes Anlass geben, wenn ein genügend grosser Teil des Pankreasgewebes zerstört ist. In 5 von den Fällen Warrens (1938) lag dem Diabetes eine akute Pankreatitis zugrunde. In meinem Material befand sich ein 68-jähriger Mann, der

an akuter Pankreatitis gestorben war. Im Krankenhaus hatte man Zucker im Harn festgestellt.

Ebenso kann ein hinreichend grosses Trauma, das Pankreasgewebe zerstört, einen Diabetes verursachen. Derartige Fälle waren nicht in meinem Material enthalten.

Ferner ist bekannt, dass in Hämochromatosefällen, die schon von Hanot und Chauffard (1882) beschrieben wurden, ein Diabetes vorkommen kann (»Bronzediabetes«). Charakteristisch für diese Krankheit sind die Veränderungen in der Leber, im Pankreas und in anderen Organen sowie das Auftreten von eisenhaltigem Pigment, Hämosiderin. In den 484 Fällen Warrens (1938) kam Hämochromatosis 9 mal zusammen mit Diabetes vor. Im Material des Verfassers gab es keine solchen Fälle.

Sonstige Organveränderungen.

Die Hypophyse. Die grosse Bedeutung der Hypophysisdrüse beim Diabetes haben vor allem Houssay (1936) und Young (1937) nachgewiesen.

Kraus (1923) stellte fest, dass die Hypophyse bei Diabetikern leichter als im Mittel ist. Insbesondere ist dies bei jungen Diabetikern und solchen mittleren Alters zu beobachten.

Nach Warren (1938) sind an der Hypophyse bei Diabetikern keine bedeutenden, konstant auftretenden Veränderungen wahrzunehmen.

In dem Material des Verfassers war die Hypophyse nur ausnahmsweise gewogen oder anderweitig erwähnt worden, sodass in diesem Zusammenhang nichts darüber auszusagen ist.

Die Nebennieren. Kraus (1923) stellte fest, dass das Gewicht der Nebennieren bei jungen Diabetikern niedriger als das normale war. In den meisten Fällen spielten atrophische und degenerative Prozesse zumal im Rindenparenchym. Bei alten Diabetikern hingegen war das Gewicht der Nebennieren erhöht und sie waren lipoidreich. Von den Fällen Warrens (1938) lagen nur in einem bedeutende Nebennierenveränderungen vor. Er ist auch der Meinung, dass den Nebennieren kein wichtiger Anteil am menschlichen Diabetes zukommt. Auf die Untersuchungen Warrens ist wegen seines grossen Materials Wert zu legen.

In dem Material des Verfassers waren die Nebennieren bei Diabetikern 66 mal und in den Kontrollfällen 79 mal gewogen worden. Als das Material nach dem Alter und dem Nebennierengewicht eingeteilt wurde, bemerkte man, dass die maximale Anzahl der

Fälle sowohl bei den Zuckerkranken (13 Fälle) als bei den Kontrollfällen (22 Fälle) auf die Gewichtsgruppe 15—16 g entfiel. Nach Uotila (1942) schwankt das Gewicht der Nebennieren bei erwachsenen Finnen zwischen etwa 14 und 15 g.

Irgendein charakteristischer Unterschied zwischen den Gewichten der Diabetes- und der Kontrollfälle wurde nicht beobachtet. In der Gruppe der Zuckerkranken wurde auch kein charakteristischer Unterschied zwischen den 21—40-jährigen einerseits und den 41-jährigen und älteren Patienten andererseits wahrgenommen. Was die sonstigen Bemerkungen über die Nebennieren ausser den Gewichtsvermerken betrifft, so konnten aufgrund derselben keine Schlussfolgerungen gezogen werden.

Die Schilddrüse. In dem Material des Verfassers wurde bei Diabetikern 44 mal und in den Kontrollfällen 47 mal etwas über die Schilddrüse erwähnt. Vor der Insulinzeit findet sich nur ausnahmsweise eine diesbezügliche Erwähnung. In beiden Materialien wurden Strumafälle festgestellt, wie folgt:

	Diabetesfälle	Kontrollfälle
Struma nodosa	9	6
Struma diff. colloides	5	8
Struma diff. parenchymatosa	3	1
Zusammen	17	15

Ein eigentlicher Unterschied zwischen den Diabetikern und den Kontrollfällen scheint also nicht zu bestehen.

Es sei erwähnt, dass Wahlberg (1938) in drei Viertel aller während der Jahre 1933—1935 im Pathologisch-anatomischen Institut der Universität obduzierten Fälle, deren Schilddrüsen dem Gewicht nach normal waren, Adenome konstatiert hat.

Unter den 48 Diabetesfällen von Kraus (1929) hatten 5 junge Diabetiker eine diffuse, 6 junge und 9 alte eine nodöse Struma.

Die Leber. Neben dem Pankreas kommt der Leber eine besonders wichtige Bedeutung im Kohlenhydratstoffwechsel und beim Diabetes zu. Die Leberverfettung beim Diabetes ist eine schon lange bekannte Erseheinung (Mead, 1749). Adlersberg und Porges (1926) hielten sie für einen regelmässigen Befund beim Diabetes. Nach Warren (1938) beträgt das normale Lebergewicht bei Er-

Tabelle VIII.

Die Lebergewichte der erwachsenen Diabetesfälle nach Altersgruppen geordnet.

Leberge- wicht g	A l t e r, J a h r e						Zusam- men
	21—30	31—40	41—50	51—60	61—70	71—80	
401—600	—	—	—	—	—	—	—
601—800	—	—	—	—	—	—	—
801—1000	—	—	1	—	—	—	1
1001—1200	1	—	1	1	1	2	6
1201—1400	3	1	1	3	3	1	12
1401—1600	2	2	—	3	8	3	18
1601—1800	4	4	3	2	1	2	16
1801—2000	1	4	—	1	4	1	11
2001—2200	4	3	1	3	1	—	12
2201—2400	3	—	—	1	—	—	4
2401—2600	1	1	—	1	1	—	4
2601—2800	—	—	—	1	—	—	1
2801—3000	2	—	—	—	—	—	2
3001—3200	—	1	—	1	—	—	2
Zusammen	21	16	7	17	19	9	89

Tabelle IX.

Die Lebergewichte der erwachsenen Kontrollfälle nach Altersgruppen geordnet.

Leberge- wicht g	A l t e r, J a h r e						Zusam- men
	21—30	31—40	41—50	51—60	61—70	71—80	
401—600	—	—	—	—	1	—	1
601—800	—	—	—	—	—	—	—
801—1000	1	—	—	—	2	2	5
1001—1200	—	1	—	2	4	3	10
1201—1400	1	2	—	3	3	2	11
1401—1600	6	4	1	3	2	2	18
1601—1800	1	5	3	5	2	—	16
1801—2000	7	2	1	1	3	—	14
2001—2200	3	1	2	—	—	—	6
2201—2400	1	1	—	1	1	—	4
2401—2600	—	—	—	1	1	—	2
2601—2800	1	—	—	—	—	—	1
2801—3000	—	—	—	—	—	—	—
3001—3200	—	—	—	1	—	—	1
Zusammen	21	16	7	17	19	9	89

wachsenen 1400—1800 g, aber beim Diabetes ist es oft vermehrt, vorwiegend unter dem Einfluss der Verfettung. Als andere das Lebergewicht steigernde Faktoren werden Glykogenspeicherung, Amyloidose, metastatische Tumoren und Zirkulationsstörungen erwähnt.

Das Lebergewicht in meinem Material, nach Altersgruppen geordnet, erhielt für die Zuckerkranken aus Tab. VIII und für die Kontrollfälle aus Tab. IX. In beiden Tabellen sind nur Personen im Alter von 21 Jahren und darüber berücksichtigt worden.

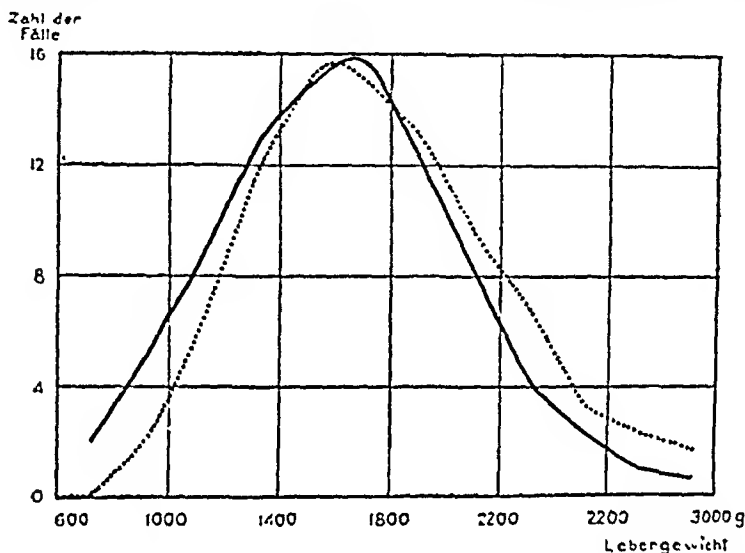


Abb. 4. Verteilung der Lebergewichte Erwachsener auf verschiedene Gewichtsgruppen.

..... Lebern der Diabetiker
 ————— Lebern der Kontrollfälle.

In den früheren Jahren ist die Leber oft ungewogen geblieben, und man hat sich mit ihrer Messung mit dem Zentimetermass begnügt.

Die Fälle verteilen sich so auf die Gewichtsgruppen, dass das Maximum beider Tabellen auf die Gewichtsgruppe 1401—1600 g entfällt. Dies entspricht ungefähr dem von Uotila (1942) angegebenen Mittelwert. Zur Veranschaulichung der eventuellen Gewichtsunterschiede zwischen den beiden Materialien habe ich (gemäß denselben Prinzipien wie in Abb. 3) in Abb. 4 die Verteilungskurven der Lebergewichte so gezeichnet, dass die Lebergewichte als Abszisse und die Anzahl der Fälle als Ordinate ange-

nommen wurden. Beim Zeichnen der Kurven sind nur die 21 Jahre alten und älteren Personen berücksichtigt worden. Aus Abb. 4 erschen wir, dass die Verteilungskurve der Diabetiker etwas mehr nach der schwereren Gewichtsseite zu verlaufen scheint als die Kurve der Kontrollfälle, und dass die Differenz um 100 g variiert.

In das vom Verfasser benutzte Material gingen Angaben über das Vorkommen von parenchymatöser Degeneration, Verfettung,

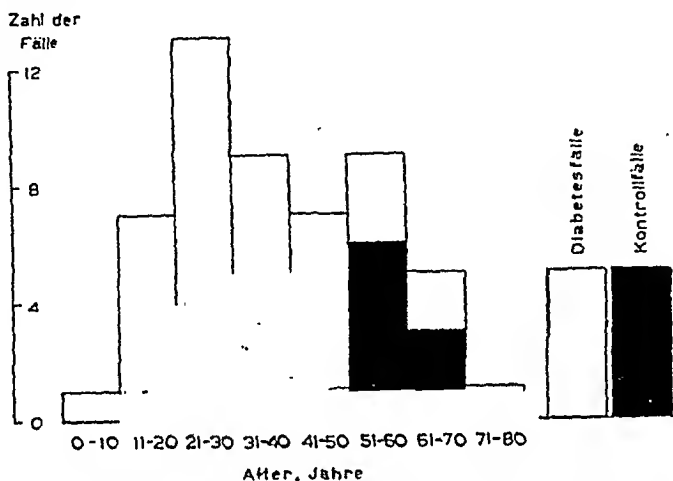


Abb. 5. Das Vorkommen von Leberverfettung bei den Diabetikern und den Kontrollfällen.

Stase und Zirrhose in der Leber der Diabetiker ein. In Tab. X und XI sind die Angaben über das Vorkommen dieser Veränderungen zusammengestellt. Wir erschen aus den Tabellen, dass die Leberverfettung deutlich öfter bei Diabetikern und relativ mehr in den jüngeren Altersklassen vorkommt (vgl. Abb. 5).

Die Gallenblase. Mehrere Forscher haben ihr Augenmerk auf das gleichzeitige Vorkommen von Erkrankungen der Gallenwege und des Diabetes gerichtet (Babinowitch, 1924, Ferger, 1931, Landé, 1931, Priesel und Wagner, 1932, Falta, 1939). Singer (1929) spricht die Erkrankungen der Gallenwege in diesen Fällen als ätiologische Ursache des Diabetes an. Bertram (1939) und Umber (1939) billigen ihnen nur die Bedeutung eines auslösenden Momentes zu, sodass der Diabetes früher zum Ausbruch kommt. Es würde sich dann am ehesten um eine Ausbreitung der Infektion von den Gallenwegen auf das Pankreas handeln, was durch die engen anatomischen Beziehungen erleichtert wird.

Tabelle X.

Das Vorkommen von Leberveränderungen bei Diabetesfällen.

	A l t e r, J a h r e									Zusammen
	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	81—90	
Deg. parench.	1	4	6	4	5	5	6	4	—	35
Verfettung	1	7	13	9	7	9	5	1	—	52
Stase	1	3	7	4	2	8	5	1	1	32
Zirrhose	—	—	—	—	2	2	3	—	—	7
Zusammen	3	14	26	17	16	24	19	6	1	126

Tabelle XI.

Das Vorkommen von Leberveränderungen bei Kontrollfällen.

	A l t e r, J a h r e									Zusammen
	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	81—90	
Deg. parench.	—	—	7	7	3	3	5	1	—	26
Verfettung	—	1	4	5	1	6	3	1	—	21
Stase	—	2	5	6	6	4	9	4	—	36
Zirrhose	—	—	2	1	—	—	1	—	—	4
Zusammen	—	3	18	19	10	13	18	6	—	87

Was das eigentliche Auftreten von Gallensteinen betrifft, so haben mehrere Forscher bemerkt, dass sie bei Diabetikern gehäuft sind. Schleusner (1938) stellte Gallensteine (oder den Folgezustand einer Cholezystektomie) in 35.2 % eines Obduktionsmaterials aus den Jahren 1914—1936 fest, dessen mittleres Alter 62.2 Jahre betrug. Der Prozentsatz ist bedeutend höher, als er für Nicht-Diabetiker gewöhnlich angegeben wird.

Wilder (1926) fand Gallensteine in 28 % seiner Diabetikeroobduktionen (insgesamt 58 Obduktionen). Warren (1938) hat das Vorkommen von Gallensteinen bei Zuckerkranken und anderen Gleichaltrigen verglichen und ist zu folgenden Ergebnissen gekommen:

	Zuckerkrankte	Nicht-Zuckerkrankte
Gallensteinfälle	139	107
Cholezystitisfälle (ohne Steine) ..	28	14
Gallenblase entfernt	1	2
Carcinoma	1	0
Fälle insgesamt	453	500

Es ist zu beachten, dass der Hauptteil von den Gallensteinen Warrens Cholesterinsteine waren, und dass er deshalb eine enge Beziehung zwischen Diabetes, Hypercholesterinämie und Gallensteinen vermutete. Joslin (1940) stellt fest, dass Cholelithiasis und Cholezystitis bei Diabetikern öfter als bei anderen Personen vorkommen, betrachtet sie aber nicht als primäre Faktoren bei der Entstehung des Diabetes.

Was mein eigenes Material betrifft, so sind die darin vorgekommenen Erkrankungen der Gallenwege in Form der nachstehenden Tabelle wiedergegeben.

	Diabetiker	Kontrollfälle
Cholesterinsteine	1	—
Pigmentsteine	1	1
Cholesterin-Pigment-Kalksteine	7	4
Sonstige und unklassifizierte Gallensteine	5	4
Gallenblase entfernt	1	—
Wandveränderungen ohne Gallensteine ..	3	2
Zusammen	18	11

Die Ergebnisse sind also, was das Verhältnis der bei Diabetikern und in den Kontrollfällen auftretenden Erkrankungen der Gallenwege betrifft, gleichgerichtet mit den von Warren dargestellten. Augenfällig ist jedoch der quantitative Unterschied zwischen dem amerikanischen Material Warrens und dem Material des Verfassers. Die Zahl der obduzierten Diabetesfälle meines Materials beträgt etwa ein Drittel von der Zahl der Diabetiker Warrens, aber die Zahl der vorkommenden Erkrankungen der Gallenwege beläuft sich nur auf ein Zehntel von derjenigen, die in Warrens Material vorkommt. Ferner fällt auf, dass in das Material

des Verfassers nur ein Cholesterinstein eingelit. Der Fall betraf eine 47-jährige Frau, deren Krankheit 4 Jahre gedauert hatte. Die Patientin starb an Koma, das durch eine eitrige Nephritis bedingt war.

Von den gallensteintragenden Diabetikern waren 10 Frauen und 4 Männer. Das Alter derselben schwankte zwischen 42 und 81 Jahren. Von den entsprechenden Kontrollfällen wiederum waren 8 Frauen und 1 Mann, die im Alter von 32 bis 81 Jahren standen.

Joslin (1940) schenkt dem gleichzeitigen Auftreten von schwerer Arteriosklerose und Erkrankungen der Gallenwege bei Diabetikern besondere Beachtung. Im folgenden stelle ich die Gallensteinfälle meines Materials, eingeteilt nach der Stärke der Arteriosklerose dar.

Arteriosklerose	Diabetesfälle	Kontrollfälle
Kelne	—	3
Schwache	4	3
Mittelstarke	3	2
Starke	7	1
Zusammen	14	9

Ferner gehen bei den Zuckerkranken in die Gruppe der starken Arteriosklerose ein Fall, bei dem die Gallenblase operativ entfernt war, und 2 von den Fällen ein, in denen die Gallenblasenwand Veränderungen ohne Steine darbot, während der dritte dieser Fälle eine schwache Arteriosklerose aufwies. Von dem Kontrollmaterial wiederum entfiel der eine Fall mit Wandveränderungen in die Gruppe der schwachen und der andere in die Gruppe der mittelstarken Arteriosklerose.

Es hat also aufgrund des vorliegenden Materials den Anschein, als ob bei Zuckerkranken mit Gallensteinen und anderen Erkrankungen der Gallenwege gleichzeitig eine Arteriosklerose getroffen wird, die stärker als in dem Kontrollmaterial ist, in dem man auch Fällen ohne Arteriosklerose begegnet.

Die Nieren. Auf die Nierenveränderungen beim Diabetes richtete schon Hanseman (1894) seine Aufmerksamkeit. In seinen 40 Diabetesfällen findet sich 22 mal die Bemerkung »Nieren typisch«. Hiermit meint er eine Vergrößerung des ganzen Organs mit glat-

ter Oberfläche. Die Rindensubstanz ist blassrot, manchmal etwas gelblich. Die Glomeruli treten als rote Punkte deutlich hervor. Die Marksubstanz ist leicht zyanotisch.

In den 183 Fällen Weichselbaums (1910) lag 9 mal eine Nephritis vor, der er jedoch keine Bedeutung beimass. Dagegen erwähnte er, dass eine fettige Infiltration der Nieren beim Diabetes gewöhnlich ist.

Kraus (1929) beschreibt eine für den Diabetes typische Nephropathie (in 24 von 48 Fällen), für die eine typische gelbrote Farbe und eine Vergrösserung der Niere charakteristisch sind. Die Veränderung tritt öfter bei jungen Diabetikern auf. Ausserdem lag bei seinen alten Fällen 4 mal eine subakute oder chronische Nephritis und 2 mal eine vaskuläre Schrumpfniere vor. Warren (1938) hält die tubuläre Nephritis für eine sehr häufige Erscheinung in Azidosefällen.

Anschliessend gebe ich eine Zusammenfassung der Nierenveränderungen, die bei den Diabetikern und in den Kontrollfällen in meinem Material beobachtet worden waren.

	Degen. adiposa	Stasis	Nephrose	Degen. parench.	Degen. amyloid.	Nephritis	Nephro- sklerose, Infarkte usw.
Diabetesfälle....	4	6	14	12	3	15	12
Kontrollfälle....	3	11	15	4	8	19	19

	Pyelo- nephritis	Tuber- kulose	Tumor	Zysten	Nephro- lithiasis	Hydro- nephrose
Diabetesfälle....	6	1	3	1	2	—
Kontrollfälle....	3	7	1	2	2	2

Wie aus obigem hervorgeht, scheint das besonders häufige Vorkommen irgendeiner Nierenveränderung für die Diabetesfälle im Material des Verfassers nicht charakteristisch zu sein. Dem Vorkommen einer eventuellen diabetischen Nephropathie im Sinne von Hanseman und Kraus ist offenbar nicht genügend Beachtung geschenkt worden, weil die Obduktionen im Laufe von 50 Jahren von sehr vielen verschiedenen Personen ausgeführt worden sind.

Die Entwicklungsfehler. Kraus (1929) betrachtet das Vorkommen verschiedenartiger Entwicklungsfehler als charakteristisch für die Diabetiker. In meinen Diabetesfällen werden einmal 2 Aortenklappen erwähnt, in den Kontrollfällen wiederum einmal ein Ren arcuatus, einmal Lien lobatum congenitale und zweimal eine daumenbeeren- bis wallnussgrosse Nebenmilz. Zu irgendwelchen Schlussfolgerungen dürften diese Befunde kaum berechtigen.

Auf Grund des vorigen möchte ich zum Schluss noch folgendes bemerken.

Wenn man das Vorkommen irgendeiner Eigenschaft z.B. bei Diabetikerobildungen studiert, vergleicht man es gewöhnlich mit den von anderen Forschern dargestellten Ergebnissen. Falls es sich um eine Eigenschaft handelt, die (wie z.B. das Organgewicht) vom Alter abhängt, können zwei verschiedene Materialien, in denen die Altersverteilung notgedrungen verschieden ist, nicht ohne weiteres miteinander verglichen werden. Es ist ja überdies bekannt, dass das Auftreten und der ganze Charakter der Krankheiten ausser vom Alter des Patienten auch von seinem Geschlecht, seiner sozialen Stellung, seinem Heimatort und vielen anderen Faktoren abhängen können. Um möglichst viele Fehlerquellen in dieser Beziehung zu vermeiden, habe ich die bei Diabetikern erhaltenen Resultate mit einem Kontrollmaterial verglichen, dessen Verteilung in bezug auf Alter, Geschlecht und Obduktionsjahr die gleiche ist wie in dem Diabetikermaterial. Es ist wahrscheinlich, dass man bei einem derartigen Vorgehen einige Eigenschaften, die angeblich bei Diabetikern gehäuft vorkommen, ins richtige Licht setzen könnte.

Trotz der grossen Bedeutung, welche die Fettsucht für den Ausbruch des Diabetes besitzt, sind die Diabetespatienten in ebenso magerem Zustand gestorben wie die Patienten des Kontrollmaterials.

Von den makroskopischen Organveränderungen der Diabetiker erweckt die Pankreasatrophie, die auch in dem von mir benutzten Material vorkommt, vielleicht die grösste Aufmerksamkeit. Welches die Ursache dieser das Organ in seiner Gesamtheit betreffenden Atrophie ist, geht nicht aus der Literatur hervor. Den Pankreassteinen und der Arteriosklerose der Pankreasgefässe, die

früher als wichtig galten, wird heute keine grosse Bedeutung mehr beigelegt. Die ersteren sind gegenwärtig relativ selten (in meinem Material z.B. nur 1 Fall). Gegen die Bedeutung der letzteren spricht ausser histologischen Untersuchungen auch das stärkere Auftreten der Atrophie in den jüngeren Jahresklassen, ein Umstand, der auch aus den Wägungsergebnissen meines Materials hervorzugehen scheint. In meinem Material sind relativ viele Fälle enthalten, in denen das Pankreas sehr klein, 30 g oder leichter war. Besonders Interesse erregen die im Schrifttum erwähnten Fälle, in denen das Pankreas, praktisch betrachtet, verschwunden ist.

Die etwas höheren Lebergewichte der Diabetiker können vielleicht von der bei ihnen auftretenden Verfettung herrühren.

Augenfällig ist ferner die geringe Zahl der Gallensteine, insbesondere der Cholesterinsteine (1 Stck) z.B. im Vergleich zu den amerikanischen Materialien. Ich werde das Vorkommen von Gallensteinen im gesamten Obduktionsmaterial des Pathologisch-anatomischen Instituts in andern Zusammenhang genauer behandeln.

Zusammenfassung.

Die makroskopischen Organveränderungen beim Diabetes in Finnland sind unter Verwendung der Obduktionsberichte aller im Verlauf von 50 Jahren im Pathologisch-anatomischen Institut der Universität Helsinki obduzierten Diabetiker behandelt worden, deren Gesamtzahl sich auf 166 beläuft. Zur Anstellung von Vergleichen wurde ein ebenso grosses Kontrollmaterial benutzt, das so eingesammelt wurde, dass man, ohne Rücksicht auf die Diagnose, für jedes Jahr, entsprechend jedem Diabetiker eine Person gleichen Alters und Geschlechtes auswählte.

Der grösste Teil der obduzierten Diabetiker war mager. Ein nennenswerter Unterschied im Vergleich zu dem Kontrollmaterial bestand nicht.

Die Bauchspeicheldrüsen der Diabetiker waren durchschnittlich etwa 25 g leichter als diejenigen der Kontrollfälle. Unter den Diabetikern gab es 22 Erwachsene mit einem Pankreasgewicht von 40 g oder darunter, unter den Kontrollfällen keinen einzigen. Eine Pankreaszirrhose kam bei Diabetikern 30 mal, in den Kontrollfällen keinmal vor. Eine Verfettung des Pankreas war bei

Diabetikern 6 mal, in den Kontrollfällen einmal zu beobachten. Unter den Diabetikern befand sich ein Fall mit Pankreasstein. Bei den Zuckerkranken kamen 2 Pankreaskarzinome vor, von denen das eine offenbar primär war und, im Caput gelegen, den Ductus verstopft, hierdurch dessen Erweiterung und eine Pankreasatrophie verursacht hatte.

Im Gewicht der Nebennieren waren zwischen den Diabetikern und den Kontrollfällen keine Unterschiede wahrzunehmen.

Verschiedene Strumaformen kamen bei Zuckerkranken 17 und in den Kontrollfällen 15 vor. Auch anderweitige Unterschiede bestanden nicht zwischen den beiden Materialien.

Die Diabetikerlebern schienen im Mittel um ca 100 g schwerer als die Lebern der Kontrollfälle zu sein. Eine Leberverfettung wurde öfter bei Diabetikern, insbesondere in den jüngeren Altersklassen gefunden.

Gallensteine scheinen bei Diabetikern etwas häufiger als bei den Kontrollfällen zu sein. Es handelte sich jedoch um wenige Fälle. Die Arteriosklerose tritt anscheinend bei den Gallenstein-diabetikern stärker auf.

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Studien über den Diabetes mellitus in Finnland.

II. Diabetisches Koma, Infektionen und Arteriosklerose im Lichte des Obduktionsmaterials.¹

Von

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(Bei der Redaktion am 16. März 1944 eingegangen).

Das diabetische Koma ist die wichtigste unter den Komplikationen des Diabetes. Dem gleichzeitigen Vorkommen von Infektionen, besonders der Tuberkulose, oder der Arteriosklerose mit Diabetes wird im allgemeinen eine grosse Bedeutung beigemessen. Es ist deshalb angebracht, in dem vorliegenden Zusammenhang auch diese Fragen zu berühren. Der Kürze halber spreche ich von »Nebenkrankheiten« des Diabetes. Auch die Todesursachen der Diabetiker, wie sie durch die Obduktionsfunde beleuchtet werden, eignen sich zu näherer Behandlung.

Wenn wir die Nebenkrankheiten des Diabetes untersuchen, ist die weitere Beleuchtung, die wir aus den Obduktionen empfangen, in den verschiedenen Fällen verschieden.

In den Komafällen können wir nicht erwarten, viele charakteristische Veränderungen zu finden, abgesehen von der wertvollen Hilfe die die Obduktion zur Aufklärung der Ursache des Komas liefern kann.

Wenn es sich um Infektionen handelt, bildet der Obduktionsbefund einen wichtigen Beitrag zu dem durch die klinische Unter-

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suchung geschaffenen Krankheitsbild, obgleich die neueren Untersuchungsmethoden wie die Röntgenuntersuchung, die Aussichten einer möglichst genauen klinischen Diagnose beträchtlich vergrößert haben.

Beim studieren der Arteriosklerose und der durch sie bedingten Organveränderungen müssen wir uns in vielen Punkten vorwiegend auf die von der pathologischen Anatomie erbotenen Mittel stützen. In diesem Zusammenhang habe ich auch den Todesursachen der Diabetiker Beachtung geschenkt, für deren Ermittlung und Bestätigung der Obduktionsbefund sehr wichtig, ja sogar von ganz ausschlaggebender Bedeutung sein kann.

Bei dieser Untersuchung habe ich mich desselben Obduktionsmaterials wie in meiner vorigen Publikation bedient.

Die Komafälle.

Das Coma diabeticum ruft keine solchen charakteristischen pathologisch-anatomischen Veränderungen hervor, aufgrund welcher man mit Sicherheit aussagen könnte, dass irgendein Patient am Koma gestorben ist. Kraus (1929) erwähnt als typische Nebensymptome des Komas das Hirnödem und den Azetongeruch der Organe. Warren (1938) führt als Folgen einer langdauernden Azidosis die tubuläre Nephritis und Blutungen in den Magendarmkanal an.

Was den Azetongeruch betrifft, so ist dem Vorkommen desselben in meinem Material offenbar nicht genügend Beachtung geschenkt worden, und er wird nur 13 mal erwähnt (meistens vom Gehirn und den Organen der Brusthöhle ausgehend).

In meinem Material sind insgesamt 63 Komafälle enthalten. Im folgenden ist das Vorkommen von Hirnödem bei diesen und den 63 ihnen entsprechenden Kontrollfällen dargestellt. Gleichzeitig wurde das Vorkommen von Ekchymosen in den beiden Gruppen verglichen.

	Komafälle	Kontrollfälle
Hirnödem	28	15
Ekchymosen	27	27

Wie man sieht, scheint in den Komafällen mehr Hirnödemen als in den Kontrollfällen aufzutreten. Im Vorkommen der Ekehymosen dagegen besteht kein Unterschied zwischen den beiden Gruppen. Ich habe auch das Vorkommen von Ekehymosen in verschiedenen Organen in dem ganzen Diabetes- und dem ganzen Kontrollmaterial verglichen, aber ein irgendwie besonders auffälliger Unterschied ist hierbei nicht zutagegetreten.

Die Infektionen.

Die akuten Infektionen. Die alte Erfahrung lehrt, dass die Diabetiker eine grosse Neigung zu bakteriellen Infektionen besitzen. Insbesondere die pyogenen Infektionen der Haut (Furunkel, Karbunkel, Phlegmonen ua.) sind sehr gewöhnlich, desgleichen die Infektionen der Harnwege. Auch die Pneumonien werden als gewöhnlich angesehen. (Vgl. z. B. Singer, 1929, Sharkey und Root, 1935, Warren, 1938, Umber, 1939, Joslin, 1940).

In meinem Material waren die verschiedenen Infektionen folgendermassen vertreten:

	Diabetiker	Kontrollfälle
Abszesse, Phlegmonen, Furunkel	15	1
Zystitis, Pyelitis, Pyelonephr.	20	17
Pneumonie	42	38
Sepsis	6	9
Cholezystitis.....	2	2
Sonstige Infektionen	14	29
Zusammen	99	96

Lediglich die erste Gruppe weist bei den Diabetikern eine deutliche Überlegenheit auf. In den zwei folgenden Gruppen sind die Unterschiede schon gering. Auch in der Totalanzahl der Infektionen sind die Differenzen nur klein.

Die Tuberkulose. Dem Vorkommen der Tuberkulose im Zusammenhang mit Diabetes schenkte seinerzeit schon Bouchardat (1875) Beachtung. Naunyn (1900) hielt die Tuberkulose für die gewöhnlichste Komplikation der Zuckerkrankheit. In seinem eigenen Material hatte er 17 % Tuberkulose gefunden. In von Noordens

(1917) Material in Frankfurt a. M. waren 5—15 % und in Wien 27 % tuberkulös. Mehrere frühere Forscher, deren Ergebnisse von Naunyn und von Noorden dargestellt werden, haben bei Diabetikeroberduktionen bedeutend höhere Prozentzahlen erhalten, nämlich:

Griesinger	42 %
Frerichs	21: 55
Windle	136: 220
Rauch	18: 42
Saundby	27 %
Otto.....	13: 35

Von Noorden war indessen der Ansicht, dass die Tuberkulose bei Diabetikern nicht öfter als bei anderen Personen auftritt, dass also die Zuckerkrankheit die Gefahr des Erkrankens an Tuberkulose kaum erhöht. Dagegen wirken die Krankheiten, wenn sie zusammentreffen, ungünstig aufeinander. Derselben Meinung sind Postma-Sprenger (1939) und Joslin (1940). Ebenso hält Lundberg (1925), dafür, dass der Diabetes eine Verschlimmerung der Tuberkulose bewirkt.

In letzter Zeit ist die Tuberkulosefrequenz, insbesondere dank der Insulinbehandlung, gesunken (Singer, 1929, Pagel und Henke, 1930, Rabinowitch, 1933, Warren, 1938, Falta, 1939, Postma-Sprenger, 1939, Joslin, 1940).

Während der Jahre 1898—1938 waren von den 15072 Diabetikern Joslins (1940) nur 364 tuberkulös. Root (1934) fand in einem 51705 Nicht-Diabetiker umfassenden Obduktionsmaterial in 22.9 % eine aktive Tuberkulose, unter 1121 Diabetikern wiederum in 28.4 %.

In Tab. I ist das Vorkommen von Tuberkulose in meinem Material dargestellt. Die Totalanzahl der Tuberkulösen, 46 aktive und 10 inaktive Fälle von 166, ist relativ hoch. Unter den Kontrollfällen ist jedoch die Anzahl der Tuberkulösen fast ebenso gross (39 aktive und 11 inaktive Fälle). Ein etwas grösserer Unterschied besteht in der Verteilung auf die verschiedenen Tuberkuloseformen. Bei den Diabetikern ist eine Lungentuberkulose III. Grades bedeutend häufiger als in den Kontrollfällen, während es unter den letzteren mehr Fälle gibt, in denen die Tuberkulose ausserhalb der Lungen auftritt. Ich habe auch die Verteilung der Tuberkulose auf die verschiedenen Altersgruppen untersucht, aber hierin keine

Tabelle I.

Das Vorkommen von Tuberkulose in dem ganzen Diabetesmaterial (166 Fälle) und bei den 166 Kontrollfällen.

Art der Tuberkulose	Diabetesfälle	Kontrollfälle
Lungentuberkulose I Grades	5	1
Lungentuberkulose II Grades	6	5
Lungentuberkulose III Grades	22	6
Lungentuberkulose mit Tuberkulose in einem anderen Organ	13	25
Tuberkulose nur ausserhalb der Lungen	—	2
Inaktive Lungentuberkulose	10	11
Zusammen	56	50

Tabelle II.

Das Vorkommen von Tuberkulose bei den 63 Komapatienten und den entsprechenden 63 Kontrollfällen.

Art der Tuberkulose	Vorinsulinära		Insulinära	
	Komafälle	Kontrollfälle	Komafälle	Kontrollfälle
Vernarbter oder eingekapselter Herd in den Lungen	4	2	1	2
Lungentuberkulose I. Grades	2	—	1	1
Lungentuberkulose II. Grades	2	1	—	1
Lungentuberkulose III. Grades	2	3	1	—
Lungentuberkulose sowie Tuberkulose in einem andern Organ	—	10	—	5
Zusammen	10	16	3	9
Keine Tuberkulose	29	23	21	15

Tuberkulose bei den Komapatienten insgesamt $13:63 = 20.6\%$

Tuberkulose in den Kontrollfällen insgesamt $25:63 = 39.7\%$

charakteristischen Unterschiede zwischen den beiden Materialien wahrnehmen können.

Als etwas Besonderes sei die Feststellung erwähnt, dass die an Tuberkulose leidenden Diabetiker nur selten Koma bekommen (Bertram, 1934, 1939). Root erwähnt in der Monographie Joslins (1940), dass diese Auffassung veraltet ist, und dass das Koma oft zusammen mit Tuberkulose bei denselben Patienten vorkommt.

Was mein eigenes Material betrifft, so habe ich die Frage aufgrund von meinen 63 Komafällen studiert. Aus Tab. II ersieht man, dass unter den Komafällen nur halb so viele tuberkulös waren als unter den entsprechenden Kontrollfällen. Wenn wir nur die schweren Phthisenfälle III. Grades sowie die Fälle von Lungentuberkulose in Betracht ziehen, wo gleichzeitig eine Tuberkulose in anderen Organen vorlag, ist der Unterschied noch bedeutend grösser.

Eine ausserhalb der Lungen lokalisierte Tuberkulose und zumal eine Tuberkulose der serösen Häute wird bei Diabetikern als selten erwähnt (Joslin, 1934, 1940, Falta, 1939). In gleichem Sinne sprechen die von mir in Tab. I dargestellten Angaben. Fälle, in denen ausser der Lungentuberkulose auch eine Tuberkulose in anderen Organen erschienen wäre, kamen bei den Diabetikern nur halb so viele vor als unter den Kontrollfällen. Eine ausschliesslich ausserhalb der Lungen lokalisierte Tuberkulose wurde bei den Diabetikern nicht beobachtet.

Die Arteriosklerose.

Die meisten Forscher sind der Ansicht, dass die Arteriosklerose bei Diabetikern gehäuft auftritt (vgl. z.B. Naunyn, 1900, Thorel, 1915, von Noorden, 1917, Joslin, 1937, 1940, Bertram, 1934, Warren, 1938, Falta, 1939 und Möllerström, 1943). Was das kausale Verhältnis der beiden Krankheiten betrifft, so sprach Naunyn die Arteriosklerose für die Ursache des Diabetes an, von Noorden wiederum umgekehrt. Nach Umber (1939) kommt dem Diabetes keine nennenswerte Bedeutung als Urheber der Arteriosklerose zu. Es handelt sich um eine zufällige Kombination einer diabetischen und arteriosklerotischen Erbanlage. Er hält es jedoch für möglich, dass die anhaltende Hyperglykämie eines schlecht behandelten Diabetes den arteriosklerotischen Prozess beschleunigen kann. Eine ähnliche Auffassung vertrat Singer (1929).

Als Ursache der Arteriosklerose bei Diabetikern betrachtete Aron (1913) den reichlichen Genuss von Speisen und insbesondere von Getränken, der die Kreislauforgane schädigt. Joslin (1937, 1940) schenkt besonders dem Fett- und Cholesteringehalt der Nahrung, des Organismus und namentlich des Blutes Beachtung und sagt: »With an excess of fat diabetes often begins and

from an excess of fat diabetics die, formerly of coma, recently of arteriosclerosis». Den Fettgehalt der Nahrung beschuldigt auch Bertram (1939). Nach Warren (1938) liegt die wichtigste Ursache in dem gestörten Kohlenhydratstoffwechsel und dem hohen Lipoidgehalt des Blutes. In diesem Zusammenhang beschränke ich mich darauf, auf die Bedeutung hinzuweisen, die den Lipoiden bei der Entstehung der Arteriosklerose auch im allgemeinen beigemessen wird (Aschoff, 1936).

Man nimmt an, dass die Zunahme der Arteriosklerose bei Diabetikern teilweise darauf beruht, dass die Zuckerkranken seit der Verbesserung der Behandlungsmethoden länger leben, sodass sich die Arteriosklerose besser bei ihnen entwickeln kann. In allerletzter Zeit scheint die Zunahme der Arteriosklerose, wenigstens in Amerika, zum Stillstand gekommen zu sein (Joslin, 1940).

Die Arteriosklerose kann auch bei sehr jungen Diabetikern auftreten. Nach Joslin (1934) ist das erste Jahrzehnt das einzige, in dem bei Diabetikern keine makroskopischen arteriosklerotischen Veränderungen angetroffen werden. Auch bei Nicht-Diabetikern kann die Arteriosklerose früh auftreten. Nach den von Jores (1924) aus dem Schrifttum eingesammelten Angaben kann die Arteriosklerose in Form von Herden in den Koronargefäßen auch bei Nicht-Diabetikern sogar schon in den ersten Nebensjahren vorkommen. Nach Priesel und Wagner (1932) hat die Arteriosklerose für den Diabetes des Kindesalters keine Bedeutung.

Die amerikanischen Forscher Warren und Joslin halten dafür, dass eine Arteriosklerose bei fast jedem Patienten vorliegt, dessen Diabetes 5 Jahre gedauert hat. Diesem Standpunkt hat sich u.a. Bertram (1939) angeschlossen. Umber (1939) und seine Schule (Leutenegger, 1932) dagegen hielten gestützt auf ein klinisches Material, die Arteriosklerose bei Diabetikern mit 5-jähriger Anamnese nicht für so gewöhnlich (65 von 133 Fällen).

Nach von Noorden (1917) tritt die Arteriosklerose der Diabetiker meistens in den Arterien der unteren Extremitäten auf, danach in den Kranzgefäßen. In den Materialien der amerikanischen Forscher steht die Sklerose der Koronargefäße und der Arterien der unteren Extremitäten ebenfalls im Vordergrund (Joslin, 1934, 1940, Warren, 1938). Nach Mönckeberg stellt die Erkrankung der linken Kranzarterie in der Regel auch bei Nicht-Diabetikern die früheste Manifestation der Arteriosklerose am

Tabelle III.

Das Vorkommen von Arteriosklerose in den Diabetesfällen.

Arteriosklerose	Alter, Jahre									Zusammen
	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	81—90	
Präinsulinära:										
keine	1	4	8	4	—	—	—	—	—	17
schwache	—	5	11	13	8	5	3	1	—	46
mittelstarke....	—	—	1	1	2	1	2	—	—	7
starke	—	—	—	—	3	1	1	—	—	5
Zusammen	1	9	20	18	13	7	6	1	—	75
Insulinära:										
keine	3	5	9	6	—	1	1	—	—	25
schwache	—	1	5	6	3	5	4	—	—	24
mittelstarke....	—	—	—	1	1	5	7	4	—	18
starke	—	—	1	—	2	4	5	3	1	16
Zusammen	3	6	15	13	6	15	17	7	1	83

Tabelle IV.

Das Vorkommen von Arteriosklerose in den Kontrollfällen.

Arteriosklerose	Alter, Jahre									Zusammen
	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	81—90	
Präinsulinära:										
keine	1	7	11	8	4	2	—	—	—	33
schwache	—	2	9	8	8	2	1	1	—	31
mittelstarke....	—	—	—	1	—	2	3	—	—	6
starke	—	—	—	1	1	1	2	—	—	5
Zusammen	1	9	20	18	13	7	6	1	—	75
Insulinära:										
keine	3	6	12	5	1	2	1	—	—	30
schwache	—	—	3	6	3	5	7	—	—	24
mittelstarke....	—	—	—	2	2	4	8	6	1	23
starke	—	—	—	—	—	4	1	1	—	6
Zusammen	3	6	15	13	6	15	17	7	1	83

Gefässsystem dar. Es sei indessen erwähnt, dass die Erkrankungen der Kranzgefässe nach dem klinischen Material des Deutschen Leutenegger (1932) die seltenste Manifestationsform der Arteriosklerose bei Diabetikern sind.

In Tab. III und IV ist das Vorkommen der Arteriosklerose in dem von mir benutzten Obduktionsmaterial dargestellt. Ich habe das Material in zwei Teile geteilt, nämlich in die Präinsulinära (1895—1922) und die Insulinära (1923—1943).

Nach der Stärke der Arteriosklerose sind die Fälle in Gruppen geteilt. Zu den »leichten« gehören die Fälle, in denen nur sklerotische Flecke an der Innenfläche der Gefässe (oder des Endokards) vorliegen. Zu den »schweren« gehören die Fälle, in denen grosse, durch die Arteriosklerose bedingte Veränderungen bestehen (Gangrän, Hirnblutung, Verstopfung der Kranzgefässe usw.).

Wie man aus den Tabellen III und IV ersieht, ist der Unterschied zwischen den Diabetikern und den Kontrollfällen nicht allzu gross. In beiden Zeitaltern finden sich unter den Diabetikern weniger solche Personen, die frei von Arteriosklerose sind. In der Präinsulinära haben die Diabetiker etwas mehr leichte Arteriosklerose als die Kontrollfälle. Im Insulinzeitalter findet sich bei den Diabetikern häufiger eine starke, bei den Kontrollfällen wiederum häufiger eine mittelstarke Arteriosklerose. Die Unterschiede sind jedoch gering.

Betrachten wir dagegen die Gangränfälle, so gewahren wir einen grösseren Unterschied, wie aus folgendem erhellt:

	Diabetiker	Kontrollfälle
Gangränen der unteren Extremität	in 12 Fällen	in 2 Fällen
Gangränen der oberen Extremität	» 1 Fall	» 0 »
Zusammen	in 13 Fällen	in 2 Fällen

Im Vorkommen der Arteriosklerose in den Kranzgefässen bestand kein erheblicher Unterschied:

	Diabetiker	Kontrollfälle
Sklerotische Punkte	in 59 Fällen	in 39 Fällen
Gefässverengung	» 18 »	» 20 »
Zusammen	in 77 Fällen	in 59 Fällen

Tabelle V.

Das Vorkommen von Arteriosklerose in den Fällen mit einer Diabetesdauer von 5 Jahren oder darüber.

Grad der Arteriosklerose: 0 = keine, 1 = schwache, 2 = mittelstarke, 3 = starke.

Todes-jahr	Alter	Ge-schlecht	Diabetes-dauer	Arterio-sklerose	Bemerkungen
1943	68	w	5.5	3	Verengung der Koronar-gefäße
1942	39	m	5	0	
"	57	m	7	3	Verengung der Koronar-gefäße
1941	81	w	25	3	Verengung der Koronar-gefäße, Gangrän des Fusses
"	62	w	10	2	
"	61	w	13	2	
1940	58	w	11	3	Verengung der Koronar-gefäße, Gangrän des Fusses
1937	47	m	6	3	
1934	23	w	7	0	Cataracta diabetica
1933	59	w	7.5	1	
1932	24	m	7.5	0	
"	44	w	10	3	Verengung der Koronar-gefäße, Gangrän des Fusses
1931	55	w	5	2	Verengung der Koronar-gefäße
1926	40	m	8	1	
1900	59	m	8	2	

In Tab. V habe ich die Angaben über das Vorkommen von Arteriosklerose bei denjenigen Diabetikern meines Materials zusammengestellt, deren Krankheit 5 Jahre oder länger gedauert hat. Nur einer der Fälle stammt aus der Präinsulinära, 3 von den Fällen sind unter 40 Jahre alt. In keinen von diesen Fällen war eine Arteriosklerose vorhanden. Bei den 40 Jahre alten und älteren Diabetikern dagegen lag in allen Fällen eine Arteriosklerose vor. Eine Gangrän bestand bei 3 von ihnen.

Die Todesursachen.

In Tab. VI habe ich die Todesursachen der Diabetiker und der Kontrollfälle im Vergleich zueinander dargestellt (die Resultate sind an Hand der klinischen Krankengeschichten kontrolliert worden).

Die überwiegend wichtigste Todesursache der Diabetiker sowohl während des Präinsulin- als des Insulinzeitalters ist das Coma diabeticum gewesen. In der letzteren Ära ist jedoch eine starke Abnahme der Komafälle zu verzeichnen. In Tab. VII gebe ich die Ursachen wieder, die wahrscheinlich die Urheber des Komas gewesen oder gleichzeitig mit ihm aufgetreten sind. Wir bemerken, dass im grössten Teil der Fälle keine Ursache für das Koma herausgebracht worden ist. Die Pneumonie und die anderen akuten Infektionen (Karbunkel, Furunkel, Abszesse, Erysipelas usw.) sind wichtige Urheber des Komas gewesen, wenngleich die Bedeutung der letzteren in der Insulinära abgenommen hat.

Tabelle VI.

Die Todesursachen aller Diabetesfälle während der Präinsulinära und der Insulinära verglichen mit den Todesursachen der Kontrollfälle.

	Diabetesfälle			Kontrollfälle		
	Präinsulinära	Insulinära	Zusammen	Präinsulinära	Insulinära	Zusammen
Coma.....	39	24	63	—	—	—
Herz- und Gefässkrankheiten						
Arteriosklerose						
des Herzen	—	5	5	2	7	9
des Gehirns	1	1	2	2	5	7
Gangrän	3	6	9	—	—	—
Art. skler. in anderen Org.	1	—	1	—	—	—
Nichtarteriosklerotische ..	—	—	—	2	2	4
Akute Infektionen						
Pneumonie	7	12	19	14	8	22
Andere Inf.	8	6	14	8	12	20
Tuberkulose	14	18	32	20	13	33
Maligne Tumoren	5	4	9	13	20	33
Nephropathieen	1	2	3	7	2	9
Andere Ursachen	2	7	9	13	16	29
Zusammen	81	85	166	81	85	166

Tabelle VII.

Die 63 Komafälle gruppiert nach der wahrscheinlichen Ursache des Komas.

	Präinsulinära	Insulinära
Keine klare Ursache	19	13
Herzinfarkt	—	1
Pneumonie	7	7
Sonstige akute Infektion	11	2
Tuberkulose	2	1
Zusammen	39	24

Wenn wir zur Betrachtung von Tab. VI zurückkehren, bemerken wir ferner, dass die Bedeutung der Arteriosklerose als Todesursache bei den Diabetikern und den Kontrollfällen gleich gross ist. Eine Gangrän als Todesursache ist jedoch nur bei den ersteren vorgekommen. Nichtarteriosklerotische Herzfehler wiederum sind ausschliesslich bei den letzteren zu verzeichnen.

Bei Behandlung der akuten Infektionen müssen wir auch die in Tab. VII dargestellten berücksichtigen und bemerken dabei, dass sie bei den Diabetikern als wichtige Todesursache fungiert haben. Die Bedeutung der Tuberkulose scheint in beiden Materialien die gleiche zu sein. Die malignen Tumoren hingegen haben in den Kontrollfällen bedeutend öfter die Todesursache gebildet. In der Gruppe »Sonstige Ursachen« kamen in den Kontrollfällen 5 mal Blutkrankheiten, 4 mal Gravidität und deren Komplikationen und 5 mal Ulcus ventriculi vor, von denen nur das letztere einmal bei den Diabetikern auftrat.

Die Verteilung der Todesursachen bei den Diabetikern aus der Insulinära ist sehr ähnlich wie diejenige, die Ponteva (1938) aus der II. Medizinischen Universitätsklinik zu Helsinki darstellt (44 Fälle). Die Verteilung der Todesursachen in dem klinischen Material von Bonsdorffs (1937) (68 Fälle) ist etwas verschieden. Seine Fälle waren Einwohner der Stadt Helsinki aus der Periode 1930—1936. In seinem Material ist die Bedeutung der Arteriosklerose grösser und diejenige der Tuberkulose geringer als in dem vorliegenden Material.

Aus dem oben angeführten geht folgendes hervor.

Von den akuten Infektionen weisen nur die pyogenen eine deutliche Häufung bei den Diabetikern auf. Auffallend ist, dass die Gesamtanzahl der Infektionen bei den Zuckerkranken kaum grösser ist als in dem Kontrollmaterial.

Das Prozent des Vorkommens der Tuberkulose ist hoch, jedoch nicht viel höher als in dem Kontrollmaterial. Die von Root mitgeteilten Zahlen sind gleichgerichtet, obwohl niedriger. Dagegen spricht mein Material dafür, dass an Tuberkulose leidende Diabetiker seltener Koma bekommen, insbesondere dann, wenn die Tuberkulose schwer ist. Root hält diese Auffassung für schon veraltet.

Besonders fällt auf, dass die Arteriosklerose die sich in mehreren anderen Ländern zu einer immer wichtigeren Nebenkrankheit des Diabetes gestaltet, bei den Diabetikern meines Materials nur wenig mehr als in den Kontrollfällen vorkommt. Lediglich Gangränen der unteren Extremität waren bei den Diabetikern bedeutend mehr zu verzeichnen. Dagegen bestanden beispielsweise in der Sklerose der Kranzgefässe nur geringe Unterschiede, ein Umstand, der hochgradig zumal von den amerikanischen Untersuchungsergebnissen abweicht.

Auch als Todesursache ist die Arteriosklerose bei den Zuckerkranken und in den Kontrollfällen gleich wichtig gewesen.

Zusammenfassung.

Für die vorliegende Publikation ist dasselbe Obduktionsmaterial wie bei meiner früheren, die Organveränderungen bei der Zuckerkrankheit betreffenden Publikation benutzt worden.

In den Komafällen kam mehr Hirnödem vor als in den entsprechenden Kontrollfällen.

Von den akuten Infektionen traten die pyogenen Infektionen bei den Diabetikern bedeutend häufiger auf als im Kontrollmaterial (15: 1). Sonstige akute Infektionen waren in beiden Gruppen ungefähr gleich stark vertreten.

Bei meinen 166 Diabetikern lag 46 mal eine aktive und 10 mal eine inaktive Tuberkulose vor, während die entsprechenden Zahlen in den Kontrollfällen 39 und 11 lauteten. Bei den Diabetikern fan-

den sich bedeutend mehr Lungentuberkulosen III. Grades, während in den Kontrollfällen öfter eine ausserhalb der Lungen lokalisierte Tuberkulose festgestellt wurde.

Unter den Komafällen machten die Tuberkulösen nur die Hälfte der in den entsprechenden Kontrollfällen nachgewiesenen Zahl aus. Schwere Tuberkuloseformen gingen relativ noch weniger in die Komafälle ein.

Das Vorkommen einer Tuberkulose ausserhalb der Lungen war bei den Diabetikern seltener als in den Kontrollfällen.

Im Vorkommen der Arteriosklerose bestanden keine allzu grossen Unterschiede zwischen den beiden Gruppen. Gangränfälle kamen jedoch bei den Diabetikern bedeutend mehr als in den Kontrollfällen vor (13: 2).

Die wichtigste Todesursache bei den Zuckerkranken war das Coma diabeticum, als dessen Urheber die akuten Infektionen eine bedeutsame Rolle spielten. Auch ohne Koma haben die akuten Infektionen eine wichtige Todesursache dargestellt. Die Arteriosklerose und die Tuberkulose sind als Todesursachen in den beiden Materialien gleich wichtig. Die malignen Tumoren dagegen haben in den Kontrollfällen bedeutend öfter die Todesursache gebildet als bei den Zuckerkranken.

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